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F O R E W O R D

ALMOST two years ago Tetrahedron , the International Journal of Organic Chemistry, was hopefully launched on the seas of world science. The reception given to this initiative has been encouraging; a medium, so broadly based, for the publication of original contributions evidently satisfied, at least in part, a very real need.

At the beginning a declaration of the ambition to achieve a high standard of the memoirs published in Tetrahedron was made. This policy has been steadily pursued and will be further implemented in the future. A certain inconvenience has been experienced due to the inclusion of shorter "Notes" and "Preliminary Communications" in Tetrahedron for the resultant inhomogeneity was unsatisfactory both for the longer and the shorter papers. It has been realised that a separation of the two would be in the interest of both and hence Tetrahedron Letters emerges as an associated but distinct publication.

Though it has been the fashion in some quarters to decry the shorter papers yet the fact is that they are rapidly increasing in number and undoubtedly lead to the progress of our science. The reason is clearly that benefits are conferred both on the authors and on other investigators. The former secure early priority in discovery and the latter get valuable information which may well be applied in directions uncontemplated by the pioneers. The essence of the matter is rapid publication and it is hoped to achieve this in Tetrahedron Letters the aim being appearance not more than two weeks after acceptance. It is confidently believed that this service will be appreciated by organic chemists and that it will be recognised as a further outstanding contribution to the dissemination of knowledge throughout the world.

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The co-operation of authors is invited in the following respects:

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(2) The Letters should be brief but not mere general summaries. Enough detail should be given to enable the reader to understand exactly what has been done.

(3) The nomenclature should as far as convenient be that adopted by the International Union of Pure and Applied Chemistry.

(4) Diagrams should be sparingly used. The inclusion of complex diagrams will inevitably lead to delays. On the other hand it is recognised that some diagrams are essential for an understanding of the Note in many cases.

It is felt that observance of these points will enable the Publisher to achieve his objective, namely the provision of widely distributed medium for the disclosure of advances in organic chemistry at the earliest opportunity.

Robert Robinson

1959

OBSERVATIONS ON SOME CARBOHYDRATE BENZYLDENE DERIVATIVES

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Chemistry Department, The University, Birmingham, 15

(Received 16 January 1958)

1959

THE formation of the new asymmetric carbon atom in the reaction of benzaldehyde (and other aldehydes except formaldehyde) with sugar derivatives to yield 5- and 6- membered cyclic acetals might be expected to yield diastereoisomers. Apparently, and as predicted,[1] only one diastereoisomer is formed in most benzylidenation reactions which afford a 6-membered cyclic acetal (1:3-dioxan derivative). The expected [2] diastereoisomer would have the phenyl group equatorial [3] to the 1:3-dioxan ring. However, in certain cases two products have been isolated and these are frequently cited as examples of distereoisomers. Thus glycero-gulo-heptitol ("α-glucoheptitol") yields [4] a mono-O-benzylidene derivative (m.p. 155-156°) which is converted to 3:5-O-benzylidene-glycero-gulo-heptitol [5] (m.p. 218°) on recrystallisation from ethanol.[4] Similarly D-perseitol (D-glycero-D-gala-heptitol) yields [6] two 1:3-5:7-di-O-benzylidene derivatives

---

[1] Angyal and Mills, Rev. Pure Appl. Chem. 2, 185 (1952); Mills, Adv. Carbohydrate Chem. 10, 1 (1956).

[2] Barton and Cookson, Quart. Rev. 10, 44 (1956).

[3] Barton, Hassel, Pitzer and Prelog, Nature, Lond. 172, 1096 (1953).

[4] Fischer, Ann. 270, 64 (1892); Ber. 27, 1524 (1894).

[5] Hann, Hess and Hudson, J. Amer. Chem. Soc. 68, 1769 (1946).

[6] Hess, Hann and Hudson, J. Amer. Chem. Soc. 70, 765 (1948).

(A, m.p. 153-155° $[\alpha]_D$ - 58.2° (pyridine); B, m.p. 280°, $[\alpha]_D$ -58.1°). Identical derivatives were obtained on methylation or benzoylation of A and B and A was converted into B by repeated recrystallisation from ethanol-pyridine. Parallel results were obtained in the L-perseitol series.[6] The facile "rearrangement" of the labile forms and the $[\alpha]_D$ values suggests polymorphism.

Through the courtesy of Dr. N.K. Richtmyer samples [6] of the 1:3-5:7-di-O-benzylidene derivatives of D- and L- perseitol were made available; the m.p.s. of these compounds were as recorded.[6] All four compounds gave indistinguishable infra-red spectra both in Nujol mulls and KBr disks. This is compelling evidence that the substances comprise two pairs of polymorphic forms not diastereoisomers. It is noteworthy that both cis- and trans- 1:3-O-benzylidene glyceritol [7] were unaffected by treatment with hot ethanol-pyridine.

From the reaction [8] of magnesium diphenyl with methyl 2:3-anhydro-4:6-O-benzylidene-α-D-allopranoside three forms of methyl 4:6-O-benzylidene -2-deoxy-2-C-phenyl-α-D-glucopyranoside were isolated (C, m.p. 163.5°, $[\alpha]_D$+ 143° ($CHCl_3$); D, m.p. 194.5°, $[\alpha]_D$ + 126°; E, m.p. 144.5°, $[\alpha]_D$ + 132°) C and D were considered to be diastereoisomeric at the acetal carbon atom and E to be a mixture of C and D. Benzoylation of C and saponification of the product gave D; recrystallisation of crude E (m.p. 139-145°) from ethanol gave a product with an even wider m.p. range.

Although the pattern of behaviour of these compounds resembles that of the di-O-benzylidene-perseitols the $[\alpha]_D$ values suggests that they are not polymorphs. Specimens of C, D and E were kindly provided for

---

[7] Baggett, Foster and Stacey, Chem. & Ind. 1229 (1958).

8 Richards, J. Chem. Soc. 2013 (1955).

examination by Dr. G.N. Richards; the m.p.s. of C and D had not changed on storage but that of E had become more diffuse (150-160°). The infra-red spectra of C, D and E in KCl disks suggested C and D to be different compounds and E to be a mixture of C and D. If, as seems probable, methyl 2:3-anhydro-4:6-O-benzylidene-α-D-allopyranoside is a pure diastereoisomer then any stereochemical difference between C and D must arise in the reaction of the epoxide compound with magnesium diphenyl.

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The reaction of benzaldehyde with glyceritol [9] represents a unique case since the relevant products, cis-and trans- 1:3-O-benzylidene-glyceritol, may be considered diastereoisomeric at either C_2 or the acetal carbon and further, intra-molecular hydrogen bonding [10] may significantly influence the amount of each isomer formed in the reaction. Similar considerations apply to the reaction of p-nitrobenzaldehyde and glyceritol.[11]

The reaction of benzaldehyde with sugar derivatives to yield diastereoisomeric 5-membered cyclic acetals (1:3-dioxolan derivatives) is well substantiated; thus methyl β-D-arabopyranoside yields [12] two 3:4-O-benzylidene derivatives isolated as the benzoates (m.p. 126-127°, $[\alpha]_D$ + 174° ($CHCl_3$); m.p. 100-102°, $[\alpha]_D$ + 214°). Methyl α-D-manno-pyranoside yields [13] two di-O-benzylidene derivatives (m.p. 181-182°, $[\alpha]_D$ + 0.9° ($CHCl_3$); m.p. 97-98°, $[\alpha]_D$ - 61.3°) as does 1:5-anhydro-D-mannitol (styracitol) [14] (m.p. 165°, $[\alpha]_D$ - 148° ($CHCl_3$);

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[9] Irvine, Macdonald and Souter, J.Chem. Soc. 107, 344 (1915).
[10] Brimacombe, Foster and Stacey, Chem. & Ind. 1228 (1958).
[11] Hibbert and Carter, J. Amer. Chem. Soc. 50, 3376 (1928).
[12] Oldham and Honeyman, J. Chem. Soc. 986 (1946).
[13] Robertson, J. Chem. Soc. 330 (1934).
[14] Asahina and Takimoto, Ber. 64, 1803 (1931).

m.p. 192-195°, $[\alpha]_D$ - 80°). If as seems likely,[1] these compounds are 2:3-4:6-di-O-benzylidene derivatives then the differences may well be due to stereochemical variations at the acetal carbons in the 1:3-dioxolan rings.

The authors thank Mr. A.S. White for measurement of the spectra and Drs. K.J. Morgan and D.H. Whiffen for helpful discussion.

ON THE STRUCTURE OF DIOSCORINE

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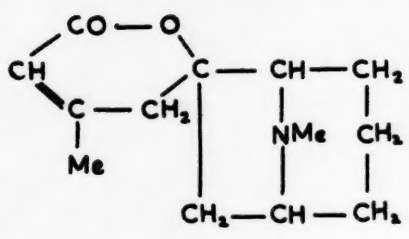
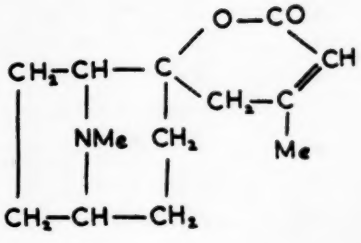
(Received 29 January 1959)

AFTER investigations by Pinder [2-7] had shown that the alkaloid Dioscorine has either structure I or II, Büchi et al.[8] presented evidence in favour



I



II

of I. It was subsequently shown by Pinder [9] that this cannot be correct, and that the correct structure must be II.

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[1] I.C.I. Fellow.

[2] A.R. Pinder, Nature Lond. 168, 1090 (1951).

[3] A.R. Pinder, J. Chem. Soc. 2236 (1952).

[4] A.R. Pinder, J. Chem. Soc. 1825 (1953).

[5] A.R. Pinder, J. Chem. Soc. 1577 (1956).

[6] A.R. Pinder, Chem. & Ind. 1240 (1957).

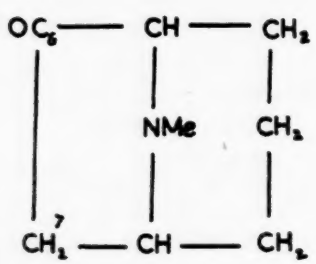
[7] A.R. Pinder, Tetrahedron 1, 301 (1957).

[8] G. Büchi, D.E. Ayer and D.M. White, XVIth International Congress of Pure and Applied Chemistry, Paris, July 1957.

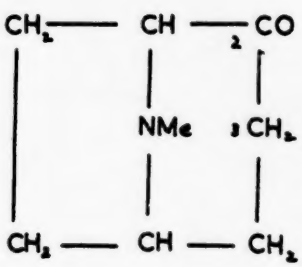
[9] J.B. Jones and A.R. Pinder, Chem. & Ind. 1000 (1958).

This structure is now supported by Büchi.[10] His earlier evidence[8] in favour of structure I was as follows:

(1) That the ketone derived by degradation of the lactone ring (i.e., III or IV) had a carbonyl band in the infra-red at 1730 cm^{-1}, 1723 cm^{-1} (CS_2)[10] and that this was in better agreement with a cyclopentanone than with a cyclohexanone structure. Pinder has already pointed out[9] that this is not so; in fact, accepted ranges[11] are 1720-1706 cm^{-1} for cyclohexanones and 1749-1745 cm^{-1} for cyclopentanones. It is relevant



III



IV

to consider more closely related compounds: the carbonyl frequency in tropinone (3-oxotropane) is at 1722 cm^{-1} (Nujol), and in 6-hydroxytropinone[12] at 1705 cm^{-1} (Nujol), 1715 cm^{-1} (CCl_4). This clearly supports the cyclohexanone structure (IV) for the ketone, and is confirmed by the position of the carbonyl band in 6-oxotropane (III),[9] which is at 1750 cm^{-1}, as expected for a cyclopentanone.

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[10] D.E. Ayer, G. Büchi, P. Reynolds-Warnhoff and D.M. White, J. Amer. Chem. Soc. 80, 6146 (1958).

[11] L. J. Bellamy, The I.R. Spectra of Complex Molecules, Methuen, London (1958).

[12] Samples were generously provided by Professor A. Stoll and Dr. N. Clauson-Kaas.

(2) That Hofmann degradation of the oxotropane (now known to be IV) methiodide occurred very readily (aqueous sodium bicarbonate at 30°). This is not referred to in Büchi's more recent communication,[10] although it becomes even more curious since 6-oxotropane, which, of the two compounds, should eliminate more readily, is unaffected by the same reagent.[9]

Thus, although the weight of the evidence [13] definitely supports Pinder's structure (II) for Dioscorine, there remains an anomalous piece of evidence against it.

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[13] The degradation product, 2-oxotropane, has been synthesised [M.R. Bell and S. Archer, J. Amer. Chem. Soc. 80, 6147 (1958)].

THE REACTION OF TRIPHENYLPHOSPHINEMETHYLENES WITH LITHIUM ALUMINUM HYDRIDE

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(Received 26 January 1959)

ALTHOUGH triphenylphosphineacylmethylenes have been known for some time,[1] Wittig's recent preparation of the simpler analogs has been of interest because of their synthetic utility.[2]

We wish to report a new reaction which these compounds undergo on treatment with lithium aluminum hydride. When the triphenylphosphinemethylenes, $(C_6H_5)_3P{=}CHR$:

(I) R=H, (II) R= $COCH_3$, (III) R=COC_6H_5,

(IV) R=$COC(CH_3)_2COCH(CH_3)_2$ [3]

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* United States Public Health Predoctoral Fellow of the National Institute of Arthritis and Metabolic Diseases, 1957 - 59.

** Contribution No. 1518 from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut.

[1] A. Michaelis and E. Kohler, Ber. Dtsch. Chem. Ges. 32, 1566 (1899).

[2] G. Wittig and U. Schollkopf, Ber. Dtsch. Chem. Ges. 87, 1318 (1954); G. Wittig, Experientia 12, 41 (1956); G. Wittig, Angew. Chem. 68, 505 (1956); F. Ramirez and S. Dershowitz, J. Org. Chem. 22, 41 (1957).

[3] Preparation and structural information are described in Ph. D. Thesis of M. Saunders, Harvard University (1956).

were stirred with excess reagent in either-tetrahydrofuran, products were obtained on hydrolysis in which hydrogen had been added to the methylene carbon and which had lost benzene.

(I) gave a liquid phosphine which yielded dimethyldiphenylphosphonium iodide upon treatment with methyl iodide (28% yield; m.p. 249.5-251°, lit.[4] 241°. Found: C, 48.9; H, 5.0; P, 9.2. Calc. for $C_{14}H_{16}PI$: C, 49.1; H, 4.7; P, 9.1%). The phosphines readily oxidized on standing in air to crystalline phosphine oxides.

(II) gave $(C_6H_5)_2P(O)CH_2COCH_3$ (18% yield; m.p. 127-129° λ_{max} 5.84 (C=O), 8.48μ (P^+-O^-). Found: C, 70.2; H, 6.3; P, 12.0. $C_{15}H_{15}O_2P$ requires C, 69.8; H, 5.9; P, 12.0%).

(III) gave $(C_6H_5)_2P(O)CH_2COC_6H_5$ (42% yield; m.p. 140-140.5°. λ_{max} 5.96 (C=O), 8.47μ (P^+-O^-). Found: C, 74.9; H, 5.6; P, 10.0. $C_{20}H_{17}O_2P$ requires C, 75.0; H, 5.4; P, 9.7%).

(IV) gave $(C_6H_5)_2P(O)CH_2COC(CH_3)_2CHOHCH(CH_3)_2$ (34 % yield; m.p. 145 - 147.5°. λ_{max} 2.96 (OH), 5.87 (C = O), 8.47 μ ($P^+ - O^-$). Found: C, 70.7; H, 7.6; P, 8.9. $C_{21}H_{27}O_3P$ requires C, 70.6; H, 7.6; P, 8.6 %).

The isolation of ketonic products after reaction in the presence of excess $LiAlH_4$ is most readily explicable in terms of an enolate salt which is resistant to further attack. Such an enolate might be formed by either attack of the $LiAlH_4$ on the phenyl group producing benzene directly or addition to the phosphorous atom giving a pentavalent intermediate which can lose benzene in a manner similar to the loss of biphenyl from pentaphenylphosphorous.[5]

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[4] A. Michaelis and A. Link, Liebigs Ann. 207, 193 (1891).

[5] G. Wittig and G. Geissler, Liebigs Ann. 580, 44 (1953).

NATURALLY OCCURRING OXYGEN HETEROCYCLICS V. [1]

MAMMEIN

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Department of Chemistry, Wayne State University, Detroit 2, Michigan

(Received 5 February 1959)

RECENT papers have been concerned with the isolation [2] and characterization [3] of mammein, a crystalline insecticidal constituent of the seeds of Mammea americana L. We should now like to record certain observations which lead to the assignment of structure I to this substance. Mammein represents the first naturally occurring coumarin [4] with a n-propyl substituent at C-4 and it is also interesting to note that a number of synthetic coumarins have been shown to exhibit insecticidal activity.[5]

Dihydromammein (II), in which the isopropylidene double bond [3] of mammein (I) has been reduced, upon heating with 5% aqueous alkali led to

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[1] Paper IV: D. Herbst, W. B. Mors, O.R. Gottlieb and C. Djerassi, J. Amer. Chem. Soc. 81, in press (1959).

[2] M. P. Morris and C. Pagan, J. Amer. Chem. Soc. 75, 1489 (1953).

[3] C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey and M. P. Morris, J. Amer. Chem. Soc. 80, 3686 (1958).

[4] For pertinent reviews see: F. M. Dean in L. Zechmeister's, Progress in the Chemistry of Organic Natural Products Vol. IX, pp. 225-291. Springer, Vienna (1952); L. Reppel, Pharmazie 9, 278 (1954); W. Karrer, Konstitution und Vorkommen der organischen Pflanzenstoffe, pp. 532-562 Birkhäuser, Basel (1958).

[5] P. Lauger, H. Martin and P. Müller, Helv. Chim. Acta 27, 892 (1944).

methyl n-propyl ketone,[6] isovaleric acid and isovalerylphloroglucinol (V).[7] These three cleavage products account for 21 out of the 22 carbon atoms of mammein and, together with the earlier reported [3] spectral results, suggest strongly that mammein is a substituted coumarin. Methylation of the residual material, after removal of the above cleavage products, furnished a crystalline, fluorescent dimethyl ether, m.p. 109-109.5°, of the composition $C_{19}H_{26}O_4$, whose ultraviolet absorption spectrum was virtually superimposable upon that [8] of 5,7-dimethoxycoumarin. The structure (XII) of this crucial degradation product was established by the following synthetic sequence:

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Pechmann condensation of isovaleroylphloroglucinol (VII)[7] with ethyl butyroacetate (VIII) furnished 4-n-propyl-5, 7-dihydroxy-6-isovaleroylcoumarin (IX) [9] (m.p. 228-229°; found: C, 67.30; H, 7.32; O, 26.23. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62; O, 26.29), which was transformed by Clemmensen reduction into 4-n-propyl-5,7-dihydroxy-6-isovalerylcoumarin (X) (m.p. 183.5-186°; found: C, 66.45; H, 7.98. $C_{17}H_{22}O_4.H_2O$ requires C, 66.21; H, 7.85.) Methylation with dimethyl sulfate and potassium carbonate provided the non-fluorescent 4-n-propyl-5, 7-dimethoxy-6-isovalerylcoumarin (XI) (m.p. 51-53°; found: C, 71.52;

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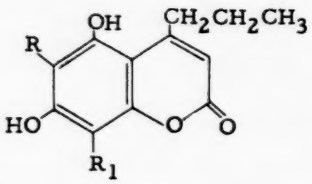
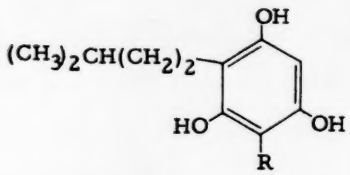
[6] This substance was first isolated in this laboratory by Dr. S.P. Marfey.

[7] T.S. Kenny, A. Robertson and S.W. George, J. Chem. Soc. 1601 (1939).

[8] H. Böhme and T. Severin, Arch. Pharm. 290, 486 (1957).

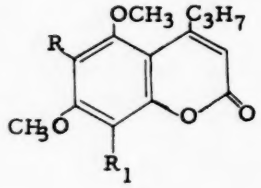
[9] We believe that ring closure in the direction of IX (rather than yielding the isomeric 8-isovaleroyl coumarin) is favored by steric considerations as well as by hydrogen bonding between the carbonyl group and the two ortho-hydroxyl groups.

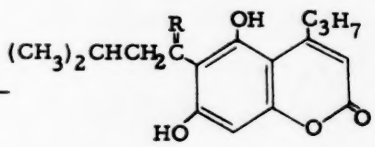




I R=$(CH_3)_2C{=}CHCH_2$; R_1=$(CH_3)_2CHCH_2CO$
II R=$(CH_3)_2CHCH_2CH_2$; R_1=$(CH_3)_2CHCH_2CO$
III R=$(CH_3)_2CHCH_2CO$; R_1=$(CH_3)_2C{=}CHCH_2$
IV R=R_1=$(CH_3)_2CHCH_2CH_2$; OH=$OCOCH_3$

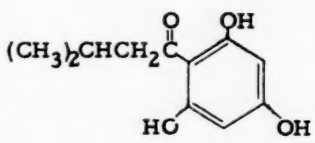
V R=H
VI R=$(CH_3)_2CHCH_2CH_2$





XI R=$(CH_3)_2CHCH_2CH_2$; R_1=H
XII R=H; R_1=$(CH_3)_2CHCH_2CH_2$

IX R=O
X R=H_2



VII

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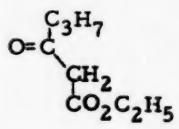

VIII

H, 8.05; O, 19.91; OCH_3, 20.08. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23; O, 20.40; 2 OCH_3, 19.49), while alkaline opening of X followed by acidification and methylation with dimethyl sulfate afforded XI as well as the fluorescent isomer 4-n-propyl-5, 7-dimethoxy-8-isovalerylcoumarin (XII) (m.p. 109-110°). The latter proved to be identical with the alkali cleavage product $C_{19}H_{26}O_4$ (Found: C, 71.59; H, 8.35; O, 29.41; OCH_3, 19.93) of dihydromammein (II), thus establishing the presence of a coumarin skeleton and the nature of the substituents at positions 4,5 and 7 of mammein. The identification of the cleavage product with the synthetic 4-n-propyl-5, 7-dimethoxy-8-isovalerylcoumarin (XII) does not necessarily imply that the isovaleryl group in dihydromammein (II) was also situated in the same position, since the coumarinic acid generated in the alkaline cleavage reaction could have cyclized in two directions as was found to be the case with synthetic X.

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In order to demonstrate that both the isovaleroyl and the isopentenyl groups of mammein (I) were located in the aromatic ring, dihydromammein (II) was subjected to Clemmensen reduction followed by acetylation and the resulting 4-n-propyl-5, 7-diacetoxy-6, 8-di-isovalerylcoumarin (IV) m.p. 103-107°; found: C, 70.59; H, 8.10; O, 21.51. $C_{26}H_{36}O_6$ requires C, 70.24; H, 8.16; O, 21.59) was heated with alkali. Acetylation of the phenolic component of this cleavage led to the triacetate of di-isovalerylphloroglucinol (VI), which was synthesized by Clemmensen reduction of isovaleryl-isovaleroylphloroglucinol [10] followed by acetylation (m.p. 104.5-105°; found: C, 67.44; H, 8.44; O, 24.08; CH_3CO, 31.61. $C_{22}H_{34}O_6$ requires C, 66.98; H, 8.69; O, 24.34; 3 CH_3CO, 32.73).

The above reactions require that mammein be represented either by

[10] W. Riedl, Ber. 85, 692 (1952).

structure I or III. We have already reported [3] that treatment of mammein at room temperature with base followed by acidification furnished a yellow isomer, isomammein, which is clearly the product arising from alternate ring closure of the intermediate coumarinic acid. For mechanistic reasons[11] (hydrogen bonding of the hydroxyl groups ortho to the isovaleroyl group in the coumarinic acid favoring ring closure in the alternate direction) and because of the similarity of the ultraviolet absorption spectra of isomammein dimethyl ether [3] and 4,8-dimethyl-5, 7-dimethoxy-6-acetyl-coumarin,[12] we assign structure III to isomammein, from which it follows that mammein is 4-n-propyl-5, 7-dihydroxy-6-isopentenyl-8-isovaleroyl-coumarin (I).

Work on other constituents of Mammea americana L. is in progress.[13]

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[11] M. Crawford and J. W. Rasburn, J. Chem. Soc. 2155 (1956); R. M. Naik and V. M. Thakor, J. Org. Chem. 22, 1240 (1957).

[12] F. M. Dean, E. Evans and A. Robertson, J. Chem. Soc. 4565 (1954). We are indebted to Dr. Dean of the University of Liverpool for this specimen.

[13] Financial assistance by the National Science Foundation and the National Heart Institute (grant No. H-2574) of the National Institutes of Health, U.S. Public Health Service, is gratefully acknowledged.

FLUORO-DERIVATIVES OF POLYCYCLIC CARCINOGENIC COMPOUNDS

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(Received 10 February 1959)

1959

FROM the strongly ortho-para-directing nature of fluorine atoms in electrophilic reactions of aromatic compounds, and the unusually large reactivity of the ortho-positions, one must conclude that the electrophilic electron localisation energies decrease strongly in the immediate neighbourhood of the fluorine-substituted carbon atom.

Therefore, if one assumes [1,2] that the determining step in the carcinogenic process in an aromatic hydrocarbon is an electrophilic reaction of the "K" region, and if one compares the electrophilic electron localisation energies of the compounds (a) with an unsubstituted "K" region and (b) with fluorine in the "K" region, one arrives at the following predictions:

First possibility: if the electrophilic substitution takes place only at the fluorinated carbon atom, the carcinogenic activity will

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[1] C.A. Coulson, Advances in Cancer Research, Vol. 1, p. 2. New York (1953).

[2] A. Pullman and B. Pullman, Advances in Cancer Research, Vol. 3 p. 117. New York (1955).

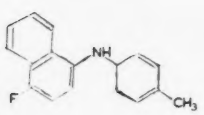
decrease, since this carbon atom will be screened by the fluorine.

Second possibility: if the substitution takes place only at the non-fluorinated atom or simultaneously on both carbon atoms, the carcinogenic activity will increase.

As it seemed interesting to compare these theoretical results with the experiment, a number of fluoro-derivatives of carcinogenic polycyclics has been synthesised. The methods of synthesis are briefly reported here.

(1) 4-Fluoro-1-naphthylamine was condensed in the presence of a trace of iodine with p- and m-toluidine, respectively. The N-p- and m-tolylderivatives so obtained (I, m.p. 74-75°; b.p. 187-189° (2 mm); II, m.p. 53° b.p. 208° (10 mm)) were cyclised with zinc chloride and acetic anhydride to 3-fluoro-5:7-dimethyl-1:2-benzacridine (III, m.p. 174°; picrate, m.p. 218-220° (dec.)) and 3-fluoro-5:8-dimethyl-1:2-benzacridine (IV, m.p. 173-175°; picrate, m.p. 210-213° (dec.)).

(Anal. Found: (III) C, 83.2; H, 5.6; N, 5.0; F, 6.8
(IV) C, 82.9; H, 5.0; N, 4.9; F, 7.2
$C_{19}H_{14}FN$ requires C, 82.9; H, 5.1; N, 5.1; F, 6.9%)



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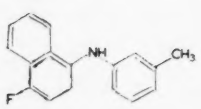

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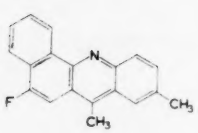

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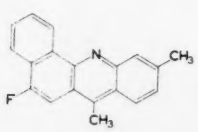

IV

(2) The synthesis of suitably methyl- and fluoro-substituted 1:2-benzanthracenes started from o-(4-fluoro-1-naphthoyl)-benzoic acid (V, from toluene, m.p. 161°), which could be prepared in 53% yield from phthalic anhydride and 4-fluoro-1-naphthylmagnesium bromide (4-fluoro-1-bromonaphthalene boiled at 108° (0.8 mm) and melted at 36°).

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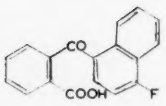

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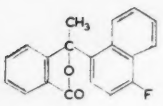

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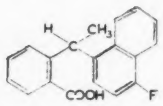

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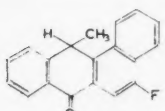

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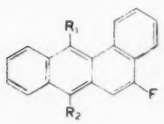

IX

Reaction of V with methylmagnesium bromide gave the lactone VI (from ethanol, m.p. 140°) which was reduced by zinc and hydrochloric acid in 40% and by phosphorus and hydriodic acid in 100% yield to 4-fluoro-1-α-(o-carboxy-phenyl -ethyl) naphthalene (VII, from nitromethane, m.p. 170.5 - 171°). Cyclisation with sulphuric acid gave in 88% yield 3-fluoro-9-methyl-1:2-benzanthr-10-one (VIII, from ethanol m.p. 130°) and reduction with zinc dust and sodium hydroxide and subsequent dehydration with alcoholic hydrochloric acid, 3-fluoro-9-methyl-1-1:2-benzanthracene (IX,

R_1=CH_3, R_2=H) (m.p. 54°, from ethanol; yield, 87%). (Anal. Found: C, 87.4; H, 5.4; F, 7.5. $C_{19}H_{13}F$ requires C, 87.7; H, 5.0; F, 7.3%). Reaction of VIII with methylmagnesium iodide gave IX (R_1=R_2=CH_3) (from cyclohexane, m.p. 94°; yield, 76%). (Anal. Found: C, 87.9; H, 5.5; F, 7.2. $C_{20}H_{15}F$ requires C, 87.9; H, 5.5; F, 6.9%).

U.V. spectra (in $CHCl_3$) III: 274 mμ (4.65); 283 mμ (4.72); 285 mμ (4.75); 296 mμ (4.70); 342 mμ (3.88); 369 mμ (3.92); 390 mμ (3.90).

IV: 264 mμ (4.52); 272 mμ (4.58); 284 mμ (4.71); 294 mμ (4.64); 322 mμ (3.83); 336 mμ (3.89); 355 mμ (3.83); 374 mμ (3.90); 395 mμ (3.95).

IX: (R_1 = CH_3, R_2 = H): 285 mμ (4.78); 295 mμ (4.38); 348 mμ (3.79); 396 mμ (3.04).

IX: (R_1 = R_2 = CH_3): 289 mμ (4.65); 300 mμ (4.68); 366 mμ (3.78).

A more detailed description of these and related experiments as well as the results of the biological testing of the compounds III, IV and IX (R_1=R_2=CH_3 and R_1=CH_3, R_2=H) will be reported elsewhere.

STEREOCHEMISTRY OF DESOXYPODOCARPIC ACID ISOMERS

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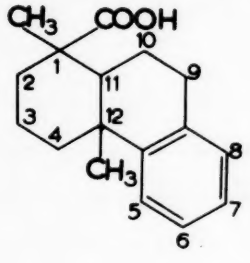
(Received 16 February 1959)

IN connexion with the assignment of definite stereochemistry to a synthetic acid (I) melting at 146-147°,[1] it became of importance to study the stereochemical behaviour of other racemates melting at 232-233°,[2] 205-207°[3] and 186-187°.[3]



I

During this investigation, a new synthesis of two epimeric acids (I) m.p. 206-207° and 232-233° having an well-defined stereochemistry has been developed along with a synthesis of DL-podocarpic acid and the present communication deals with these studies.

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[1] N.N.Saha, B.K.Ganguli and P.C.Dutta, Chem. & Ind. 412 (1956).

[2] R.D.Howarth and R.L.Barker, J. Chem. Soc. 1299 (1939).

[3] W.E.Parham, E.L.Wheeler and R.M.Dodson, J. Amer. Chem. Soc. 77, 1166 (1955).

2-(β-Phenethyl)-3 methyl-3-carbomethoxycyclohexanone, b.p. 178-180°/0.6 mm. (Calc. for $C_{17}H_{22}O_3$; C, 74.45; H, 8.03; Found: C, 74.15; H, 8.06); yellow 2:4-dinitrophenylhydrazone, m.p. 163° (Calc. for $C_{23}H_{26}O_6N_4$; N, 12.33; Found: N, 12.50) was obtained in a good yield through the conjugate addition of hydrocyanic acid to 2-(β-phenethyl)-3-methyl- Δ^2-cyclohexenone,[4] followed by alkaline hydrolysis and esterification. The above ketoester was reacted with methyl-magnesium-iodide and the crude carbinol on subsequent dehydration with anhydrous oxalic acid in toluene [5] yielded a slightly yellowish liquid b.p. 150-160°/0.15 mm, which was found to be a complex mixture because of the presence of a strong γ-lactonic band (5.67μ), a strong ester band (5.77μ) and a weak hydroxyl band (2.86μ), as revealed by infra-red studies. The above mixture on cyclisation with polyphosphoric acid [6] on steam-bath for 1½hr afforded a crystalline acidic product and a liquid neutral material. The acidic product on crystallisation from ethylacetate-ethanol afforded an acid, m.p. 232-233° (Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; Found: C, 78.66; H, 8.64), methyl ester m.p. 131-132° (Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; Found: C, 79.39; H, 8.95). (Prof. R.D.Haworth was kind enough to compare the mixed melting points of the acid 232-233° and the methyl ester 131-132°, with his samples, and found no depression.) From the mother-liquor another acid was isolated, m.p. 206-207° (Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; Found: C, 78.85;

[4a] G.Stork and A.W.Burgstahler, J. Amer. Chem. Soc. 73, 3544 (1951);

[4b] N.N.Saha, P.N.Bagchi and P.C.Dutta, J.Amer.Chem.Soc. 77, 3408 (1955).

[5] T.Weil and D.Ginsberg, J. Chem. Soc. 1291 (1957).

[6] F.E.King, T.J.King and T.G.Topliss, Chem. & Ind. 113 (1956).

H, 8.63), methyl ester m.p. 84-85° (Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; Found: C, 79.02; H, 8.90). These two acids showed a tendency to form a eutectic, melting at 190-192° and afforded 1-methylphenanthrene on dehydrogenation with 10% Pd-C. The neutral product on hydrolysis with 10% butanolic potassium hydroxide solution afforded the acid, m.p. 206-207°, besides some other low melting product, which was not further investigated. The unhydrolysed product yielded some methyl ester, m.p. 131-132°, described earlier.

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The synthesis of DL-podocarpic acid has been achieved from this ester, through the introduction of the hydroxyl group in the 6-position.[7] It was allowed to react with acetyl chloride in presence of aluminium chloride in nitrobenzene. The ketonic product was isolated through semicarbazone, which on decomposition yielded 6-acetyl-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, m.p. 133-134° (from methanol), λ_{max}^{alc} 259 mμ, log ε 4.17 (Calculated for $C_{20}H_{26}O_3$: C, 76.40: H, 8.34; Found: C, 76.41; H, 8.55), orange 2:4-dinitrophenylhydrazone m.p. 234-235° (Calculated for $C_{26}H_{30}N_4O_6$: C, 63.15; H, 6.07; Found: C, 63.16; H, 6.31). The above ketone on oxidation with perbenzoic acid in chloroform yielded DL-methyl podocarpate acetate m.p. 125-126° (Calc. for $C_{20}H_{26}O_4$: C, 72.72; H, 7.87; Found: C, 72.35; H, 8.01), which on hydrolysis with ethanolic potassium hydroxide solution gave DL-methyl podocarpate m.p. 193°, (Calc. for $C_{18}H_{24}O_3$: C, 75.0; H, 8.33; Found: C, 75.02; H, 8.50). On hydrolysis with 10% ethylene glycolic potassium hydroxide the methyl ester gave DL-podocarpic acid, which crystallised from ethylacetate-petroleum ether and melted at 266-268° alone or mixed with an authenic sample (through the

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[7] E.Wenkert and B.G.Jackson, J.Amer.Chem.Soc. 80, 217 (1958).

courtesy of Dr.T.J.King).

The methyl ester (m.p. 131-132°) on oxidation with chromic acid in acetic acid solution [8] afforded 9-keto-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, which crystallised from methanol in two polymorphic forms, m.p. 124-125°, λ_{max}^{alc} 249 mμ, log ε 4.07, (Calc. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; Found: C, 75.44; H, 7.97) and m.p. 146-147° (Calc. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; Found: C, 75.07; H, 7.90); orange 2:4-dinitrophenylhydrazone m.p. 219-220° (Calc. for $C_{24}H_{26}O_6N_4$: N, 12.02; Found: N, 12.26).

On oxidation under identical conditions the methyl ester, m.p. 84-85° yielded 9:10-diketo-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, a bright-yellow crystalline solid (from petroleum ether-benzene) m.p. 129-130°, λ_{max}^{alc} 288 mμ, log ε 3.87; (Calc. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.67; Found: C, 72.30; H, 6.82). The diketone was converted to the corresponding enol-acetate by refluxing with acetic-anhydride and fused sodium acetate. The crude gummy enol-acetate, λ_{max}^{alc} 259 mμ, log ε 4.04; on catalytic hydrogenation [8] with 10% Pd-C in acetic acid solution containing a drop of 60% perchloric acid, gave the solid methyl ester, m.p. 131-132° (Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; Found: C, 79.16; H, 8.68) alone or mixed with the sample described before.

The formation of the mono-keto- and diketo-esters on oxidations [8] and the subsequent transformation through the enol-acetate, conclusively proved that the epimeric centres at C-1 are identical in both acids and these differ only at ring junction, i.e. the acid with m.p. 232-233°, being

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[8] E.Wenkert and B.G.Jackson, J. Amer. Chem. Soc. 80, 211 (1958).

trans-locked [8,9] or desoxypodocarpic acid and the acid with m.p. 206-207° is cis-locked or cis-desoxypodocarpic acid.

The acid (I) with melting point 146-147° has now been proved to be cis-desisopropyldehydroabietic acid.[10] The remaining isomer, desisopropyldehydroabietic acid remains to be described and it is unlikely that the acid, melting at 186-187°, which is again derived from the 10-keto acid,[3] can be assigned this stereochemistry, because of the improbability of the epimerisation at C-1 through Wolff-Krishner reduction. The possibility of this acid being an eutectic cannot be altogether ruled out and this is being investigated.

The author is indebted to Prof. P.C.Dutta for his kind interest and valuable suggestions, and also to Mr. P.Bagchi for his kind encouragement during this work. Grateful thanks are also due to Mrs. Chhabi Dutta, of the Microanalytical Laboratory of the University College of Science, Calcutta and to Mr. A.B.Dutta of this laboratory for analyses.

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[9] G. Stork and W.J.Schwlenberg, J. Amer. Chem. Soc. 78, 250 (1956).

[10] N.N.Saha, B.K.Ganguli and P.C.Dutta, J. Amer. Chem. Soc. in press (1959).

ABSTRACTS OF SOME OF THE PAPERS TO BE PUBLISHED IN FUTURE ISSUES OF TETRAHEDRON

BISCHLER-NAPIERALSKI REACTION—II

SYNTHESIS OF SOME KETONIC ISOQUINOLINES

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(*Received* 25 *August* 1958)

Abstract—Ethylene ketals of the type (I) cyclise in presence of phosphorus pentoxide in pyridine to give the ketal (II) which on hydrolysis yields 1-phenyl-6:7-dimethoxy-4-oxo-3:4-dihydro*iso*quinoline (III). 1-(4-oxo-*cyclo*hexyl)-6:7-dimethoxy-3:4-dihydro*iso*quinoline (VIII) and 2-oxo-3-methyl-9:10-dimethoxy-1:2:3:4:6:7-hexahydro-11bH-benzo[a]-quinolizine (XV) were also synthesised.

THE REACTION OF SULPHUR AND SULPHUR COMPOUNDS WITH OLEFINIC SUBSTANCES—XIII

THE MECHANISM OF INTERACTION OF SULPHUR WITH (+)-LIMONENE

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Abstract—The reaction of sulphur with (+)-limonene (I) to give the hydrocarbons (II) and (III), and the cyclic sulphides (+)-(IV), (−)-(V), and optically inactive (VI), as demonstrated by Weitkamp,[1-3] is shown to be uniquely consistent with a recently advanced polar mechanism of olefinic sulphuration.[5,6]

THE MAGNITUDE OF ELECTRONIC ISOTOPE EFFECTS

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(*Received* 20 *September* 1958)

Abstract—Secondary isotope effects, i.e. kinetic isotope effects in reactions where the bond to the labeled atom is not broken, are now being widely used for investigations of organic reaction mechanisms. In a recent paper, Halevi[1] has discussed secondary hydrogen isotope effects, and has suggested that there is an inductive contribution to such isotope effects. In particular, he suggests that there is

more facile electron release from a C—D bond than from a C—H bond. The purpose of this communication is to examine in more detail some of the evidence cited by Halevi, and to estimate the theoretical limitations on such an effect.

METHYLATION OF ALCOHOLS WITH DIAZOMETHANE

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(*Received* 22 *September* 1958)

Abstract—Alcoholic hydroxyl groups were methylated by diazomethane in the presence of catalytic amounts of fluoboric acid (FBA). Primary aliphatic and unhindered secondary alcohols gave 84–98% yields of methyl ethers, while tertiary and moderately hindered secondary alcohols afforded lower yields. The order of reactivity in the methylation of the isomeric butyl alcohols, as determined in competition experiments, was $n > s > t$, and of the epimeric cholestanols, 3 $\beta(e) > 3\ \alpha(a)$. The highly hindered alcoholic hydroxyl groups of *iso*borneol was not methylated by the new reagent. The methylation of weakly acidic phenols was catalyzed by FBA. The new methylation reaction was used to prepare dierctly methyl ethers of desoxycorticosterone and of testosterone, and to convert ascorbic acid selectively to its 2:3:6-trimethyl ether.

THE CONSTITUTIONS OF ATROVENETIN AND OF SOME RELATED HERQUEINONE DERIVATIVES

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(*Received* 26 *September* 1958)

Abstract—Deoxy*nor*herqueinone and atrovenetin have been shown to be identical. On the basis of spectral evidence these compounds, and related substances, have been characterised as substituted 9-hydroxyperinaphthenones. This conclusion has been confirmed by oxidative degradation to the appropriate naphthalic anhydrides as well as by further oxidation to nitrococussic acid. The constitution of an important oxidation product, $C_{15}H_{14}O_9N_2$, obtained by the action of nitric acid on atrovenetin has been established. On the basis of this and other evidence the constitutions of atrovenetin and certain of its transformation products have been elucidated.

A STUDY OF THE HYDROGEN BONDS BETWEEN THE NITRO-GROUP AND THE HYDROXYL OR AMINO-GROUPS IN SUBSTITUTED NITROPARAFFINS

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(*Received* 10 *July* 1958)

Abstract—The ultra-violet absorption epectra of many nitro paraffin derivatives containing hydroxyl and or amino groups, do not show a maximum (260–270 mμ) typical of the nitro group. This is attributed to the formation of six-membered chelate rings by internal hydrogen bonds between the nitro and hydroxyl or amino groups. The presence of such hydrogen bonds also produces a bathochromic effect, the maxima being shifted towards longer wavelengths (270–285 mμ); but *two* hydroxyl groups or one secondary amino group are necessary to transform the normal maximum of the nitro group into a bend. This is considered as new evidence for the electrostatic nature of the hydrogen bond. Hydrogen bonds between nitro and hydroxyl or amino groups also produce a bathchromic effect; the corresponding maxima being shifted towards longer waves (270–285 mμ).

STUDIES ON ARGENTINE PLANTS—XVII

THE STRUCTURE OF FAGARINE II

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(*Received* 29 *September* 1958)

Abstract—The structure of Fagarine II, an alkaloid from *Fagara coco* (Gill.) Engl., has been elucidated through its transformation into tetra-hydro-psuedo berberine.

THE STRUCTURE OF ψ-CONHYDRINE

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(*Received* 17 *October* 1958)

Abstract—The three-dimensional structure, except for the absolute configuration, of ψ-conhydrine has been determined in an X-ray diffraction study of ψ-conhydrine hydrobromide. In agreement with recent chemical evidence, the OH and propyl groups are found to be *trans* to each other, and in the equatorial position relative to the saturated six-membered ring. The unit cell is orthorhombic in the space group D_2^4-$P2_12_12_1$, contains four $C_8H_{18}NOBr$, and has dimensions $a = 15{\cdot}15$, $b = 9.28$, $c = 7{\cdot}72$ A. Refinement, including anisotropic thermal motion, has yielded values of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}109$ and $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}056$ for the 920 observed reflections.

MECHANISM OF REACTION OF METHYLENE WITH THE CARBON–HYDROGEN BOND

EVIDENCE FOR DIRECT INSERTION

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(*Received* 17 *September* 1958)

1959

Abstract—The photolysis of diazomethane in 2-methylpropene-1-^{14}C leads predominantly to 2-methylbut-1-ene-1-^{14}C whether the reaction be run in the liquid or gas-phase. This result is the first unequivocal evidence in support of mechanisms involving direct insertion of methylene into the carbon–hydrogen bond.

In the gas-phase, recovered 2-methylpropene shows a small amount of mixing of radioactivity while the 2-methylbutene-1 shows as much as 8 per cent. The intervention of free radicals as a side-reaction is indicated.

THE "POSITIVE HALOGEN" REACTION BETWEEN BENZOTRICHLORIDES AND POTASSIUM IODIDE

RELEVANT MECHANISTIC AND STERIC ASPECTS

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(*Received* 27 *October* 1958)

Abstract—The "positive halogen" reactions of 2:3:4:5-tetrachlorobenzotrichloride and perchlorotoluene with potassium iodide in aqueous acetic acid, at 100°, have been investigated. In the case of the perchlorotoluene the products are the two isomeric perchlorostilbenes along with some 2:3:4:5:6-pentachlorobenzylidene chloride. The chief product of the reaction of 2:3:4:5-tetrachlorobenzotrichloride with potassium iodide is α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl; considerable amounts of the two isomeric α:2:3:4:5:α′:2′:3′:4′:5′-decachlorostilbenes have been isolated. Under the same conditions the α:α:2:3:4:5:α′:α′:2′:3′:4′:5′-dodecachlorobibenzyl reacts with potassium iodide to give the corresponding decachlorostilbenes.

When the reaction of perchlorotoluene with potassium iodide is performed in aqueous acetic acid containing toluene the yield of 2:3:4:5:6-pentachlorobenzylidene chloride is greatly increased and benzyl iodide is formed.

The mechanisms of these reactions are discussed. It is shown that the results are consistent with the occurrence of the reaction through the intermediate α:α-dichlorobenzyl radicals and α:α:α′:α′-tetrachlorobibenzyls, the latter being formed by dimerization of the former.

The ultra-violet absorption spectra of the geometric isomers of α:α′-dichlorostibene, α:2:3:4:5:-α′:2′:3′:4′:5′-decachlorostilbene and perchlorostilbene are recorded and interpreted. It is shown that the higher-melting isomerides have the *trans* configuration and that, as a result of the strong steric interaction between the *alpha* chloride atoms and the *ortho* atoms, there exists strong inhibition to resonance in the *trans* forms.

ANHYDROBIISATIC ACID

6:12-OXA-5:6:11:12-TETRAHYDROPHENHOMAZINE-6:12-DICARBOXYLIC ACID

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(*Received* 4 *November* 1958)

Abstract—Anhydrobiisatic acid (IVa), a new type of compound containing the phenhomazine ring system, has been obtained by self-condensation of isatic acid—(*o*-aminophenyl)glyoxylic acid—. The structure of this acid has been established and derivatives have been prepared. N:N′-Dimethyl-anhydrobiisatic acid (IVc) has been resolved into optically active components.

STRUCTURE OF PIPERIDINO-HEXOSE-REDUCTONE

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(*Received* 6 *November* 1958)

Abstract—The structure of piperidino-hexose-reductone, first described by Hodge and co-workers, was clarified by degradation reactions. Dihydro-anhydro-piperidino-hexose-reductone, obtained from piperidino-hexose-reductone in a clear way, was synthesized by reacting 1-methyl-4-chloro-*cyclo*penten(1)-ol(2)-one(3) with piperidine.

CHEMISTRY OF THE PODOCARPACEAE—I

CONSTITUENTS OF THE HEARTWOOD OF *PODOCARPUS SPICATUS*

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(*Received* 10 *November* 1958)

Abstract—Quercetin and a new *iso*flavone, podospicatin, have been isolated from *Podocarpus spicatus*. Podospicatin trimethyl ether has been shown to be 5:6:7:2′:5′-pentamethoxy*iso*flavone.

CHEMISTRY OF THE PODOCARPACEAE—II

THE ISOLATION OF GENISTEIN FROM *PODOCARPUS SPICATUS* AND THE CONSTITUTION OF PODOSPICATIN

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(*Received* 10 *November* 1958)

1959

Abstract—Genistein has been isolated from the heartwood. Podospicatin has been shown to have the constitution 5:5′:7-trihydroxy-2′:-6-dimethoxy*iso*flavone.

SUR LA SYNTHÈSE DU DIBENZO[A,I]PYRÈNE, DU TRIBENZO[A,EI]PYRÈNE, ET DE NOUVEAUX HOMOLOGUES DU NAPHTO[2,3-A]PYRENE

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(*Received* 6 *November* 1958)

Résumé—Le dibenzo[a,i]pyrène (I) a été synthétisé à partir du benzo[a]pyrène par condensation avec l'anhydride succinique en position 1, réduction de l'acide cétonique obtenu en acide γ-1-benzo[a]-pyrényl-butyrique, cyclisation en 4-céto-1:2:3:4-tétrahydro-dibenzo[a,i]pyrène, réduction de cette cétone en 1:2:3:4-tétrahydro-dibenzo[a,i]pyrène, et déshydrogénation. D'autre part, la synthèse du tribenzo[a,e,i]pyrène à partir de l'octahydroanthracène symétrique a été réexaminée, et celle de deux nouveaux homologues du naphto[2,3-a]pyrène est décrite.

Abstract—The synthesis of dibenzo[a,i]pyrene is reported, starting from benzo[a]pyrene, obtained by condensation of succinic anhydride in position 1, followed by reduction of the resulting keto acid to γ-1-benzo[a]pyrenylbutyric acid, and cyclisation to 4-keto-1:2:3:4-tetrahydrodibenzo[a,i]pyrene; the latter ketone was reduced to 1:2:3:4-tetrahydrodibenzo[a,i]pyrene, which was then dehydrogenated. Further, the preparation of symmetrical octahydroanthracene has been re-examined, and the synthesis of two new homologues of naphtho[2,3-a]pyrene is described.

LES FACTEURS ÉLECTRONIQUES DANS LA RÉACTION DE FORMYLATION DES HYDROCARBURES AROMATIQUES CONDENSÉS

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(*Received* 6 *November* 1958)

Résumé—On montre, par l'étude de la formylation de plusieurs hydrocarbures aromatiques condensés

qu'à l'interieur de chaque classe déterminée d'hydrocarbures, la facilité de formylation est une fonction croissante de l'indice de valence libre sur le sommet qui entre en reaction. Cette règle permet de prévoir, outre la réactivité des hydrocarbures eux-mêmes, également celle des diverses positions à l'intériéur de chacune de ces molécules. On applique ces observations à l'étude du tribenzo[a,c,j]-naphtacène et du phénanthro[2,3-a]pyrène, qui donnent chacun un seul aldéhyde, conformément à la théorie, laquelle indique, comme positions privilégiées, le sommet 17 dans le premier cas, et le sommet 6 dans le second cas.

Abstract—A study of the formylation of several condensed aromatic hydrocarbons shows that within each class of such hydrocarbons, the reactivity increases with the free valence index of the position to be substituted. This rule makes it possible to predict not only the behaviour of the hydrocarbons themselves, but also that of the various positions inside each molecule. These considerations are applied to tribenzo[a,c,j]naphtacene and phenanthro[2,3-a]pyrene, each of which gave a single aldehyde, in accordance with the theory, the formylation site predicted being position 17 in the first case, and position 6 in the second.

SYNTHESE DU 1:6-ANHYDRO-GALACTOSE

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(*Received* 6 *November* 1958)

Abstract—1:6-anhydro-β-D-galactopyranose has been synthesised from galactose in a 70 per cent yield. Purification of intermediate derivatives was made unnecessary.

Résumé—La synthese du 1:6-anhydro-β-D-galactopyranose a été réalisée avec un rendement global de 70% à partir de galactose et sans isolement des produits intermédiaires.

ETUDES CINETIQUES DES REACSIONS DE SOLVOLYSE DE CHLORURES D'α-PHENYLETHYLE SUBSTITUES

EQUATIONS DE HAMMETT, WINSTEIN-GRUNWALD ET TOMMILA

C. MECHELYNCK-DAVID et P. J. C. FIERENS

(*Received* 6 *November* 1958)

Abstract—The kinetic study of the solvolysis of *m*-CH_3, *p*-CH_3, *m*-OCH_3, *p*-Cl, *m*-Cl and *p*-F substituted α-phenylethyl chlorides has been carried out in the following media:

water 20·5%	dioxane 79·5%	
water 49·3%	dioxane 50·7%	
water 66·66%	dioxane 33·33%	
water 5·3%	dioxane 25·8%	formic acid 69·7%
water 6·1%	dioxane 39·8%	formic acid 54·1%
water 5·8%	dioxane 60·2%	formic acid 34·0%

Correlation of solvolysis rates has been made with the equations of Hammett, Winstein–Grünwald and Tommila.

DIE KONFIGURATION DER CARBONESTERGRUPPE UND DIE SONDEREIGENSCHAFTEN DER LACTONE

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(*Received* 19 *November* 1958)

Zusammenfassung—Die Carbonestergruppe vermag in 2 Plankonfigurationen aufzutreten. Die Siedepunkte, Dipolmomente und RG-Konstanten der alkalischen Hydrolyse der homologen aliphatischen ω-Lactone (VII, n = 4 bis 16) lehren, dass die Ringstruktur bei VII, n = 4–7 die energiereiche *cis*-Konfiguration erzwingt, während VII, n = 10–16 wie offenkettige Ester *trans*-konfiguriert sind. VII, n = 8, 9 nehmen eine Übergangsstellung ein. Die leichte Lactonhydrolyse sowie die elektrophile Aktivität des ω-Kohlenstoffs sind charakteristisch für das *cis*-Carbonestersystem.

Abstract—The ester group exists in 2 planar configurations. The boiling points, dipole moments and rate constants of alkaline hydrolysis of the homologous aliphatic ω-lactones (VII, n = 4–16) show that the ring structure forces VII, n = 4–7 into the energetically rich *cis*-configuration; the members n = 10–16 assume the *trans*-configuration of the open-chain esters, while when n = 8, 9 an equilibrium is adopted. The easy lactone hydrolysis as well as the electrophilic activity of the ω-carbon atom are characteristic of the *cis*-ester structure.

BOND LENGTHS AND BOND ENERGIES IN CONJUGATION AND HYPERCONJUGATION

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(*Received* 21 *November* 1958)

Abstract—Dewar's arguments to the effect that all evidence for the existence of appreciable effects of π-electron resonance in the ground states of conjugated and hyperconjugated molecules is inconclusive, and that all observed effects are explainable as a result of differences in hybridization in carbon σ bond orbitals, are examined. It is shown that the C—C bond-length shortenings predicted by up-to-date π-electron theory are not as great as usually supposed, and that the corresponding predicted *lengthenings* of C=C and C≡C bonds are almost *nil*. It is concluded that Dewar is partly right in supposing that the lengths of conjugated and hyperconjugated C—C single bonds are determined, to a greater extent than previously supposed, by the states of hybridization of the carbon σ bond orbitals. However, there seems to be no justification for Dewar's assumption that resonance shortenings are negligible. Tentative formulas for the contributions of resonance and hybridization are given, also a similar formula for the shortening of conjugated or hyperconjugated C=C bonds in the cumulenes. Bond angles and hybridization are discussed, and the probable existence of marked deviations from ideal trigonal and digonal hybridization, often in opposite directions for C—H and C—C or C=C carbon σ orbitals, is emphasized. These differences may help to explain why C—H bonds are shortened less than C—C bonds involving supposedly similar hybrids.

Rather general bond energy formulas are given which assume additivity of bond energies but with a different bond energy for each hybrid type of C—H or C—C (or C=C) bond. It is shown that these reduce to the usual simple formula which ignores differences in hybrid type under not unplausible assumptions which, however, are at fault in neglecting polar energies (i.e. ionic-covalent resonance

energies), especially in CH bonds. Dewar's assumption that CH bond energies are essentially independent of hybridization, and his consequent conclusion that observed stabilization energies in conjugated systems are due entirely to strengthened hybrid C—C bonds and not at all to π-electron resonance energy, is difficult to justify, especially in view of the expected importance of polar energies in CH bonds. A table of predicted polar energies for C—H and C—C bonds involving various hybrid C—C σ orbitals is given. The estimation of π-electron energy in C_3H_4, and of π-electron conjugation energy in butadiene, some energy data for twisting, are discussed. Diphenyl and *s-cis* butadiene are compared.

The relative importance of π-electron resonance and hybridization in determining the dipole moments of conjugated and hyperconjugated molecules are discussed. While any conclusive theoretical calculation would in most cases be extremely complicated, there seems to be no good reason to doubt that π-electron resonance makes important contributions. Very strong evidence from nuclear magnetic resonance data is cited in support of usual current beliefs as to the role of π-electron resonance in charge distribution in conjugated and hyperconjugated molecules. Other evidence, including dipole moments in agreement with π-electron resonance theory predictions for molecules like and azulene where no differential hybridization effects should contribute, is cited.

A STUDY OF LEUCOANTHOCYANIDINS OF PLANTS—II

(+)LEUCOCYANIDIN FROM THE GUM OF BUTEA FRONDOSA

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(*Received* 9 *September* 1958)

Abstract—A (+)leucocyanidin has been isolated from the gum of *Butea frondosa*, its acetate and methyl ether prepared and studied. The leucocyanidin is 5:7:3′:4′-flavan-3:4-diol. The methyl ether and the acetate have also been prepared by borohydride reduction of taxifolin tetramethyl ether and taxifolin respectively.

α-HYDROXYALKYLIDEN-LACTON-UMLAGERUNG—IX

SYNTHESE DES D,L-IRIDOMYRMECINS UND VERWANDTER BICYCLISCHER LACTONE

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(*Received* 23 *October* 1958)

Zusammenfassung—Es wird über allgemeine anwendbar Synthesen berichtet, die zum D, L-Iridomyrmecin und ihm verwandter bicyclischer γ- und δ-Lactone führen.

Abstract—Generally applicable synthesises which lead to D, L-Iridomyrmecin and related bicyclic γ and δ-lactones are reported.

REACTION MECHANISMS IN REDUCTIONS BY METAL–AMMONIA SOLUTIONS

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(*Received* 18 *November* 1958)

Abstract—The mechanism is discussed of the reduction of monobenzenoid compounds by means of metals and acohols in liquid ammonia. Contrary to claims in the literature[1] *iso*quinoline and dibenzothiophene are both readily reducible by this method.

1959

STEREOCHEMISTRY OF THE REDUCTION OF TROPINONE

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(*Received* 5 *December* 1958)

Abstract—Tropinone has been reduced under various conditions of time, temperature, solvent and reducing agent. The stereoisomeric composition of the reduction product was determined by infra-red spectrophotometry. The results indicate the participation of kinetic and thermodynamic factors in the stereoisomeric course of the reduction, the former depending upon the effective size of the reducing species. An assignment of the order of size of reducing species in particular solvents is made.

The stereoisomeric composition of the product of equilibration is independent of the reagent and the temperature in the systems studied.

GEWINNUNG UND EIGENSCHAFTEN EINIGER TITANORGANISCHER VERBINDUNGEN

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(*Received* 25 *November* 1958)

Zusammenfassung—Durch die Zusammenwirkung des Titan-tetrachlorids mit den Alkonolen wurde eine Reihe von titanorganischen Verbindungen wie $TiCl_3OR$ gewonnen,

(wo R = *iso*$C_3H_7^-$; *sed* $C_4H_9^-$; *cyclo*C_6H_{11}; *tert* C_4H_9)

Es ist dabei festgestellt worden, das die Verbindungen wo R das *secund.* oder *tert.* Radikal ist, im Gegensatz zu denen mit *primären* Radikalen, sich als unstabielen erweisen Während der Aufbewahrung bei Zimmertemperatur unterliegen sie einer schnelleren, bei 0° etwas langerer Zersetzung unter Bildung HCl, des Olefines und Halogen-alkylen. Den festen Rückstand bildet Titan-chloroxyd, das einen wirksamen Katalysator für Propylen, *iso*Butylen und Styrol–Polymerisation darstellt, wobei den Polymerisationsprozess Bildung der niedermolekularen Produkte begleitet. Das erwähnte

Titanchloroxyd gilt als ebenso aktiver katalysator beim Olefin-Hydrochlorieren.

Abstract—The action of $TiCl_4$ on alcohols gives compounds of the type $Ti(OR)Cl_3$ where R = *iso*$C_3H_7^-$, *sec*.$C_4H_9^-$, *tert*.C_4H_9 and *cyclo*C_6H_{11} Compounds where R is a *secondary* or *tertiary* group as distinct from a *primary* group are unstable, decomposing on keeping at room temperature and slowly at 0° yielding HCl, an olefine and alkyl halide and a residue of titanium oxychloride. The latter is a very active catalyst for the polymerisation of propylene *iso*butylene and styrene forming polymers of low molecular weight. Titanium oxychloride is also an active catalyst in the addition of HCl to olefines.

SYNTHESES WITH PYRIMIDINE-LITHIUM COMPOUNDS

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(*Received* 27 *October* 1958)

Abstract—The principles of the preparation, reactivity and use of organolithium compounds is briefly discussed in relation to recent work with N-heterocyclic derivatives. The synthesis of thymine-$C^{14}H_3$ and 5-ethyluracil from a pyrimidine-lithium intermediate, and the separation of uracil and thymine by ion-exchange chromatography, are described. It is shown that such syntheses can be carried out with compounds containing active hydrogens by taking advantage of the higher reactivity of lithium-carbon bonds, and this is illustrated in a synthesis of thymidine from 5-bromodeoxyuridine.

SYNTHESIS OF D- AND L-*ISO*IRIDOMYRMECIN AND RELATED COMPOUNDS

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(*Received* 12 *December* 1958)

Abstract—Starting from D-citronellal of natural origin, D-iridodial and D-*iso*iridomyrmecin were synthesised.* The latter furnished, on oxidation, a *nepetalinic acid*, which was the enantiomorph of a degradation product of nepetalactone. A mixture of the two specimens afforded a *racemate* of higher melting point.

L-Citronellal, obtained (Boake, Roberts & Co.) by a series of chemical transformations from pinene was similarly converted into L-iridodial and L-*iso*iridomyrmecin. The latter was identical with the natural product from *Iridomyrmex nitidus*.

ASYMMETRIC ANNELLATION EFFECTS—PART II

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(*Received* 29 *December* 1958)

Abstract—The comparison of the U.V. absorption spectra of acenes, 1:2-3:4-dibenzacenes and tetra-

benzacenes show a strong asymmetric annellation effect. This is explained on the basic assumption that an aromatic sextet or benzenoid ring can transfer only two electrons to another ring. Three benzenoid rings can thus produce an induced aromatic sextet in an included ring of the type of the central ring in triphenylene.

The synthesis of tetrabenzotetracene is described.

1959

ASYMMETRIC AND SYMMETRIC ANNELLATION EFFECTS—PART III

BENZOCORONENES

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(*Received* 29 *December* 1958)

Abstract—1:2-5:6-Dibenzocoronene (IV) was obtained from 1:2-4:5-8:9-tribenzopyrene (II) via the dianhydride (III). 1:2-4:5-Dibenzopyrene (V) condensed twice with maleic anhydride. The resulting dianhydride (VI) gave 1:2-benzocoronene (VII) on decarboxylation. 1:12-*o*-Phenyleneperylene (X) was obtained by a zinc dust melt from the quinone (VIII). The annellation effects passing from triphenylene and perylene to the benzocoronenes indicate the presence of a triphenylene complex within the electronic fine structure of coronene.

ANTHRAQUINONE AND ANTHRONE SERIES—XXIII

THE NON-IDENTITY OF 1:3:8-TRIHYDROXY-2-HYDROXYMETHYL-ANTHRAQUINONE WITH VERSICOLORIN AND A SYNTHESIS OF DAMNACANTHOL AND DAMNACANTHAL

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Abstract—1:3:8-Trihydroxy-2-hydroxymethylanthraquinone has been synthesised by hydroxymethylation of 1:3:8-trihydroxyanthraquinone and shown to be different from versicolorin, the colouring matter isolated by Hatsuda and Kuyama from *Aspergillus versicolor*. Damnacanthol and damnacanthal, the colouring matters of the roots of *Damnacanthus major* and *D. indicus* have been synthesised by a new route.

A THEORY FOR THE STEREOSPECIFIC POLYMERIZATION OF PROPYLENE OXIDE BY FERRIC CHLORIDE

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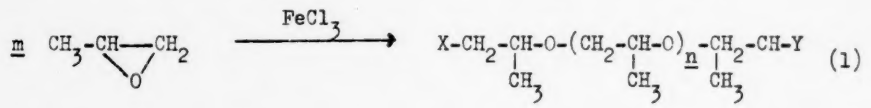
1959

THE polymerization of d,l-propylene oxide under the catalytic influence of ferric chloride may be described grossly by equation (1) in which X and Y represent terminal units, possibly Cl, OH or an unsaturated group.



$$\underline{m}\ CH_3\text{-}CH\text{---}CH_2 \xrightarrow{FeCl_3} X\text{-}CH_2\text{-}\underset{CH_3}{CH}\text{-}O\text{-}\left(CH_2\text{-}\underset{CH_3}{CH}\text{-}O\right)_{\underline{n}}\text{-}CH_2\text{-}\underset{CH_3}{CH}\text{-}Y \qquad (1)$$

Although the catalyst for the reaction and the gross structure of the polymer are unexceptional, the stereochemistry of the polymerization is extraordinary. Under the conditions which have been utilized for the polymerization, about 30-40 per cent of the polymeric product from d,l-propylene oxide is the isotactic [1] variety in which essentially all of the asymmetric carbons of a given polymer molecule possess the same configuration.[2] Thus, the optically inactive crystalline polymer consists of a mixture of all d- and all l-polymer molecules.

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[1] G. Natta, J. Polymer Sci. 16, 143 (1955); G. Natta and P. Corradini, Makr. Chem. 16, 77 (1955); C. W. Bunn and E. R. Howells, J. Polymer Sci. 18, 307 (1955).

[2a] H. Staudinger, Hochmolekulare Organische Verbindungen p. 295. Springer, Berlin (1932); [b] U.S. Pat. 2,706,181 (April 12, 1955), M. E. Pruitt and J. M. Baggett (to the Dow Chemical Co.); U.S. Pat. 2,706,182 (April 12, 1955), M. E. Pruitt, J. M. Baggett, R. J. Bloomfield and J. H. Templeton (to the Dow Chemical Co.), cf. Chem. Abstr. 49, 2395 (1955).

Price and coworkers [3,4] have shown that the polymer formed from l-propylene oxide with ferric chloride catalyst possesses the same specific rotation as that which results from l-propylene oxide using potassium hydroxide as catalyst, a clear indication that the ferric chloride-catalyzed polymerization proceeds with retention of configuration at the asymmetric center. Thus, it becomes necessary to assume that in the polymerization of d,l-epoxide the growing chain reacts selectively with that enantiomer which becomes involved in the initial stages and also that epoxide opening occurs by front-side displacement at the asymmetric carbon of the epoxide.

Based on the observations that solid gradually separates from the polymerization mixture and that the crystalline polymer possesses a higher average molecular weight than the amorphous product, it has been proposed [4] that stereospecificity is consequential to heterogeneity and is dependent on the generation of an asymmetric surface. The purpose of this note is to indicate an alternative and simpler explanation which derives from the availability of a reasonable, stereoselective mechanism for reaction in solution and which is not dependent on complex surface effects (although these might pertain). The essential features of the process are formalized in Fig. 1. In this scheme the activity of the catalyst is associated with the well-known tendency of iron to form octahedral complexes and the initial step is the reaction of ferric chloride with a molecule of propylene oxide, the d-form, for example, and some terminating

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[3] C. C. Price, M. Osgan, R. E. Hughes and C. Shambelan, J. Amer. Chem. Soc. 78, 690 (1956).

[4] C. C. Price and M. Osgan, J. Amer. Chem. Soc. 78, 4787 (1956).

group X to give the unstable complex I.[5] This is converted reversibly by co-ordination with a second propylene oxide molecule to the octahedral complex II. Complex II may react internally by attack of the nucleophilic alkoxide donor group on the nearby epoxide ring, specifically by displacement at the asymmetric carbon atom with retention of configuration,

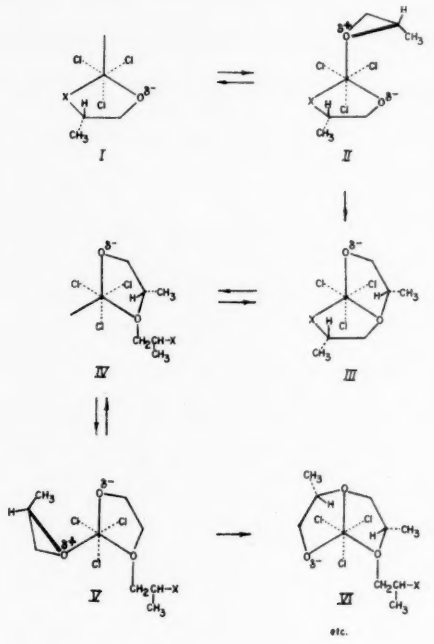

FIG. 1.

to form complex III in which the first and second units have been joined.

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[5] The five-co-ordinated intermediates in Fig. 1 are represented as possessing the tetragonal pyramid arrangement. This type of structure seems to be favored generally over the trigonal bipyramid form in SN1 reactions of octahedral complex ions; see F. Basolo and R. G. Pearson, Mechanisms of Inorganic Reactions, Chap. 5. John Wiley, New York (1958).

To the extent that the transition state for this reaction resembles the product in structure, the conversion of II to III will be more facile when the second unit is derived from the same enantiomer of propylene oxide as was the first, i.e. d as specified above, since this leads to a folded system of two cis-fused five-membered rings in which both methyl substituents are situated external to the fold, free of serious steric repulsions and both equatorial*.[6] If the second unit is derived from the other enantiomer, l-propylene oxide, a much less stable structure would result and it is suggested that instead of forming a new chelate ring the l-propylene oxide dissociates making room for the more reactive d-enantiomer. Complex III rearranges to IV which co-ordinates reversibly with another monomer unit to give V. If the third monomer unit is the d-isomer, V is converted rapidly to VI, otherwise dissociation to IV takes place. Additional monomer units unite with the growing chain by the process represented by III → VI. According to this interpretation formation of the polymer involves three orthogonal valences of the octahedral metal ion which co-ordinate singly and in turn with monomer units as the polymer is removed from the catalyst by dissociation of one donor group at a time. Construction of the polymer takes place cyclically about these three catalytic valences with constant control over the asymmetry of each unit being appended, a unique feature of this mechanism.

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[6] The five-membered chelate rings derived from 1,2-disubstituted ethanes are puckered to the extent that the substituents on carbon possess about 80 per cent axial or equatorial character (designated as axial* or equatorial*, respectively). For a detailed discussion of the geometry of such chelates and of stereospecific effects therein, see E. J. Corey and J. C. Bailar, Jr., J. Amer. Chem. Soc. In press.

1959

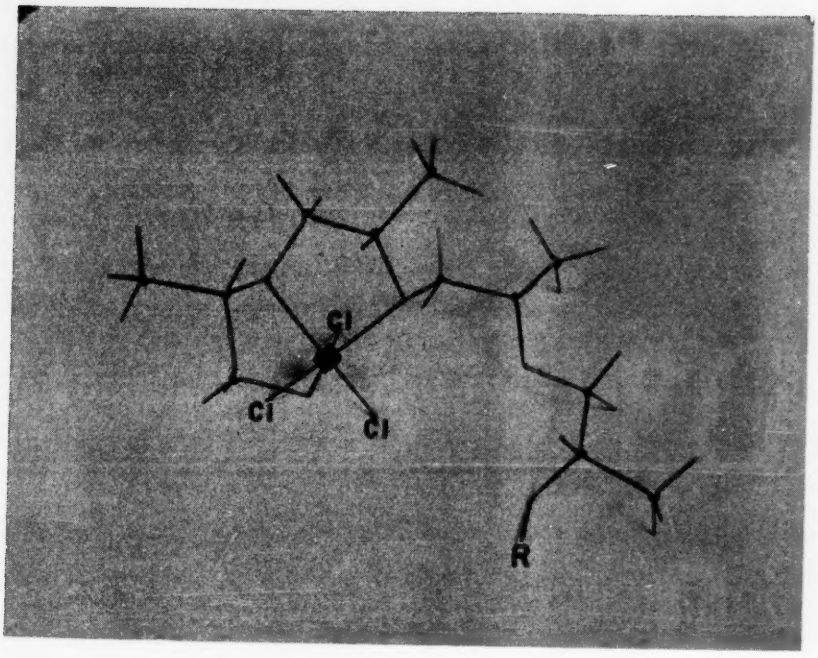

FIG. 2.

A model of complex VI is shown in Fig. 2 to illustrate the geometry of this type of intermediate and the preference for incorporation of units having the same configuration.

It is also conceivable that the polymerization might take place by a process similar to that above, but involving four of the iron valences which lie in the same plane. Here again, a cyclic addition-unwinding process in which new monomer units are added one at a time as the formed polymer units unwind is possible. Consideration of the structures involved in this process, however, makes it seem doubtful that such a polymerization would be very specific and hence this mechanism may be discounted. Other possibilities involving five or six of the iron valences can be discarded with confidence both because they do not account at all for the observed stereospecificity and because they do not present a sterically favorable reaction path.

Formation of isotactic polymer from propylene oxide has also been observed with other catalysts, e.g., aluminum isopropoxide-zinc chloride and titanium alkoxide-zinc chloride. Although these reactions are considerably less stereospecific than in the case of ferric chloride, it is possible that three of the metal valences (probably tetrahedral) are involved in co-ordination with the reactants, in a fashion analogous to the process in Fig. 1.

THE STRUCTURE OF CASSAIC ACID

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(Received 27 February 1959)

1959

IN 1955 Humber and Taylor [1] established the location of the α,β-unsaturated carboxyl function in cassaic acid and suggested structure I (without stereochemical designations) for this substance, which is obtained along with N-dimethyl-ethanolamine by hydrolysis of the Erythrophleum alkaloid cassaine.[2] The recent correlation of vouacapenic acid with cassaic acid [3] demonstrates the identity of the carbon skeletons in these two compounds, and evidence for the transfusion of rings A and B in both acids has also been provided.[3] We wish at this time to report observations that conclusively prove the correctness of the speculations of Humber and Taylor regarding the structure of cassaic acid.

Ozonization of cassaic acid as the acetate methyl ester affords II, m.p. 169-170°, $[\alpha]_D$ -16° (ethanol) (Found: C, 72.03; H, 8.74. $C_{20}H_{30}O_4$ requires C, 71.82; H, 9.04). The latter product undergoes epimerization on passage over alumina and furnishes III, m.p. 150.5-151.5°, $[\alpha]_D$ -26°

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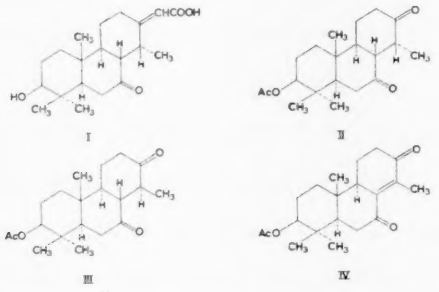
[1] L. G. Humber and W. I. Taylor, J. Chem. Soc. 1044 (1955); see also R. Tondeur, Dissertation, E. T. H., Zurich (1950).

[2] L. Ruzicka and G. Dalma, Helv. Chim. Acta 22, 1516 (1939).

[3] F. E. King, T. J. King, and J. M. Uprichard, J. Chem. Soc. 3428 (1958).

(ethanol) (Found: C, 71.86; H, 9.23). Bromination of III followed by dehydrobromination yields IV, m.p. 186.5-187.5°, $[\alpha]_D$ -7° (ethanol) (Found: C, 71.97; H, 8.54. $C_{20}H_{28}O_4$ requires C, 72.26; H, 8.49), ν_{max} 1718, 1678 cm^{-1} ($CHCl_3$), which exhibits ultraviolet absorption, λ_{max} 266.5 mμ, ϵ 10,800, characteristic of an enedione. III is regenerated from IV by mild treatment with zinc and acetic acid. The relationship of the keto group of cassaic acid to the previously located [2] acid side chain is thereby established.



I II III IV

The further details of structure are revealed by total synthesis of compounds III and IV in optically inactive form. Methylation of 6-methoxy-2-tetralone by the enamine procedure,[4] and condensation of the resulting monomethyl derivative with dimethylaminobutanone methiodide yields 2:3:4:9:10:12-hexahydro-7-methoxy-12-methyl-2-oxophenanthrene, m.p. 106-108°.[5] Dimethylation of this ketone by the conventional procedure [6]

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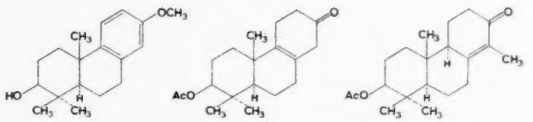
[4] G. Stork, R. Terrell and J. Szmuszkovicz, J. Amer. Chem. Soc. 76, 2029 (1954).

[5] F. H. Howell and D. A. H. Taylor, J. Chem. Soc. 1248 (1958).

[6] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, J. Chem. Soc. 1131 (1957).

followed by reduction with lithium aluminum hydride furnishes the expected unsaturated alcohol, m.p. 127-128° (Found: C, 79.35; H, 8.64. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88), Which is further converted into V, m.p. 140-141° (Found: C, 78.84; H, 9.60. $C_{18}H_{26}O_2$ requires C, 78.79; H, 9.55), by catalytic hydrogenation over palladium. Compound V undergoes Birch reduction to the corresponding dihydro derivative, m.p. 139-139.5° (Found:



V VI VII

C, 77.98; H, 10.21. $C_{18}H_{28}O_2$ requires C, 77.21; H, 10.21), which on acetylation and treatment with oxalic acid in aqueous ethanol yields the β,γ-unsaturated ketone VI, m.p. 103.5-104.5° (Found: C, 75.06; H, 9.01. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27). Reaction of this substance with methyl iodide in the presence of potassium tert.-butoxide affords VII, m.p. 136-137°, λ_{max} 249 mμ, ε 17,500, ν_{max} 1730, 1664 cm^{-1} (CS_2) (Found: C, 75.28; H, 9.46. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50), which gives the racemic modification of IV, m.p. 165-165.5°, λ_{max} 266 mμ, ε 11,300, ν_{max} 1718, 1678 cm^{-1} ($CHCl_3$) (Found: C, 71.97; H, 8.38), on oxidation with chromium trioxide in acetic acid at 60°. The infrared spectra ($CHCl_3$ soln.) of the synthetic sample and of that derived from natural sources are identical. Reduction of d,l-IV with zinc and acetic acid gives d,l-III, m.p. 158-160° (Found: C, 71.90; H, 8.83), the infrared spectrum of which is likewise identical with that of the corresponding optically active product. The above facts strongly support the stereochemical assignments of formula I.

The details of this work and of additional experiments not here reported will be published shortly. The financial support of the National Heart Institute, National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

1959

A SYNTHESIS OF α-ANHYDROTRIMETHYLBRAZILONE

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WE wish to record a synthesis of α-anhydrotrimethylbrazilone (I) that was carried to the penultimate stage in 1947. Condensation of 1,3-dimethoxybenzene and veratroyl chloride in boiling benzene with aluminium chloride afforded an excellent yield of 2-hydroxy-4,3',4'-trimethoxybenzophenone (II), instead of the tetramethoxy-compound reported [1] to result from this reaction below 40°. This preparation of the phenol (II) appears to be superior to those previously described.[2,3]

Condensation of the phenol (II) with bromoacetone and treatment of the product with alkali gave 2-acetyl-3-(3',4'-dimethoxyphenyl)-6-methoxycoumarone (III), which may be regarded as a dihydro-α-anhydrotrimethylbrazilone. Bromination of this ketone with N-bromosuccinimide proceeded slowly, giving a non-crystalline bromo-compound that afforded α-anhydrotrimethylbrazilone (I) in poor yield on treatment with aluminium chloride in benzene. The low yield of (I) may be attributed at least in part to the production of nuclear as

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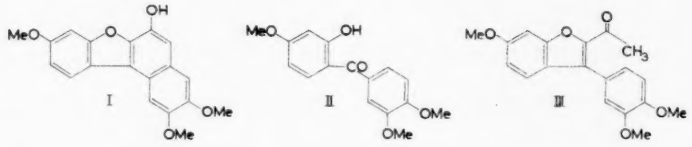
[1] P. C. Mitter and P. K. Paul, J. Indian Chem. Soc. 8, 271 (1931).

[2] J. N. Ray, S. S. Silooja and P. R. Wadha, J. Indian Chem. Soc. 10, 617 (1933).

[3] P. C. Johnson and A. Robertson, J. Chem. Soc. 2331 (1950).

well as side-chain brominated derivatives of (III) during the treatment with N-bromosuccinimide, and nuclear bromination appeared to be the main reaction with bromine, since the bromo-compound in that case gave no α-anhydrotrimethylbrazilone on treatment with aluminium chloride.

Friedel-Crafts condensations of α-halogenoketones with aromatic compounds,[4,5] and a synthesis of α-anhydrotrimethylbrazilone,[3] have both previously been reported.



EXPERIMENTAL

2-Hydroxy-4,3',4'-trimethoxybenzophenone. A solution of veratroyl chloride (10.5 g) in dry benzene (30 ml) was added to a boiling mixture of 1,3-dimethoxybenzene (7.0 g), anhydrous aluminium chloride (10 g) and dry benzene (25 ml), and the resulting mixture was heated under reflux for 1½ hr. The benzene was removed and the hard brown aluminium complex was decomposed with ice and hydrochloric acid. The solid product was collected, washed with dilute sodium carbonate and water, and recrystallised from ethanol, when 13 g (87%) of 2-hydroxy-4,3',4'-trimethoxybenzophenone was obtained as very pale yellow needles m.p. 141° (lit. m.p. 141°[2] 140°[3]). The 2:4-dinitrophenylhydrazone was obtained as dark red needles, m.p. 230°

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[4] A. Collet, Bull. Soc. Chim. 17, 506 (1897).

[5] J. P. Mason and L. I. Terry, J. Amer. Chem. Soc. 62, 1622 (1940).

(lit.[3] m.p. 231°). (Found: C, 56.1; H, 4.4; N, 11.7. Calc. for $C_{22}H_{20}O_8N_4$: C, 56.4; H, 4.3; N, 11.9%).

2-Acetyl-3-(3',4'-dimethoxyphenyl)-6-methoxycoumarone. 2-Hydroxy-4,3',4'-trimethoxybenzophenone (5 g), anhydrous potassium carbonate (10 g) and redistilled bromoacetone (12 g) were heated together under reflux in dry ethyl methyl ketone (50 ml) for 2½ hr. The solvent was removed and the residue shaken with warm 10% aqueous sodium hydroxide for 1 hr, to cause internal condensation of the initial phenoxyacetone derivative. During this time the oily product rapidly solidified. The solid was collected, washed well with water and recrystallised from ethanol, when 5 g (88%) of 2-acetyl-3-(3',4'-dimethoxyphenyl)-6-methoxycoumarone was obtained as large canary yellow plates, m.p. 153.5° (Found: C, 69.8; H, 5.6. $C_{19}H_{18}O_5$ requires: C, 69.9; H, 5.5%). This substance was insoluble in aqueous alkalis and gave no colour with ferric chloride.

The 2:4-dinitrophenylhydrazone was obtained as dark red plates, m.p. 192° on recrystallisation from benzene. (Found: C, 59.0; H, 4.1; N, 11.1. $C_{25}H_{22}O_8N_4$ requires: C, 59.3; H, 4.3; N, 11.1%).

This condensation could not be effected with chloroacetone under the same conditions unless sodium iodide was added to the reaction mixture to generate iodoacetone *in situ*, in which case the product stubbornly retained a brown colour, although the m.p. was easily raised to 153.5°.

α-Anhydrotrimethylbrazilone. 2-Acetyl-3-(3',4'-dimethoxyphenyl)-6-methoxycoumarone (0.150 g), N-bromosuccinimide (0.075 g) and benzoyl peroxide (0.012 g) were boiled under reflux in dry carbon tetrachloride (15 ml) for 24 hr, exposed to ultraviolet light for the first 2 hr. The reaction mixture was cooled and washed four times with equal quantities

of water, dried over sodium sulphate and evaporated. The resulting dark yellow resin (which contained reactive bromine, since it reacted with sodium iodide in acetone, with precipitation of sodium bromide) was dissolved in dry benzene (15 ml) and powdered aluminium chloride (0.10 g) was added to the solution. The mixture was heated under reflux on the steam bath for 5 min and allowed to stand at room temperature for 5 hr. The aluminium complex was decomposed with dilute hydrochloric acid, the benzene layer and solid matter were removed, washed with water and then extracted twice with 5 ml portions of 10% aqueous sodium hydroxide. Acidification of the alkaline extract afforded a brown solid (0.025 g) which on crystallisation from ethanol afforded α-anhydrotrimethylbrazilone as yellow-brown plates, m.p. 197° alone or mixed with an authentic specimen prepared from trimethylbrazilone.

THE STRUCTURE OF ACONITINE

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Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.

(Received 26 February 1959)

THE alkaloid aconitine $C_{34}H_{47}O_{11}N$ is the most important and complicated representative of the class of aconitum alkaloids. The confusing and contradictory chemical studies on aconitine before 1900 have been reviewed by Schulze.[1] Subsequent studies covering the first half of the 20th century, which led only to the clarification of the functional groups, have been reviewed again by Stern.[2]

We now wish to propose the complete structure of aconitine (I) in which the only ambiguity is that a methoxyl and hydroxyl may have to exchange positions. We shall start elaborating the argument by showing that the structure of the C-D ring system of aconitine (II) differs from the recently deduced [3] structure of the C-D ring system of delphinine (III) only by the presence of an additional hydroxyl.

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[1] H. Schulze, Arch. Pharm. 244, 136, 165 (1906).

[2] E. S. Stern, The Alkaloids, Chemistry and Physiology (Edited by R. H. F. Manske and H. L. Holmes) Vol. IV. Academic Press, New York (1954).

[3a] K. Wiesner, F. Bickelhaupt and Z. Valenta, Tetrahedron 4, 418 (1958); [b] K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia In press.

We have first of all established that pyrooxonitine is a ketone. This is supported by the fact that the hydrolysis product of pyrooxonitine, pyrooxonine, already described by Majima [4] shows a carbonyl maximum at 1718 cm^{-1} corresponding to a keto group in a six-membered ring. The infrared examination of pyrooxonitine of course can provide no corroboration of its ketonic character because of the presence of the strong ester peak in the same region. However, the rotatory dispersion curve of pyrooxonitine shows unambiguously its ketonic character by its typical peak at 343 mμ $[\alpha]$ = -1020.

On this finding we based the hypothetical partial structure (II) of aconitine which contains an additional hydroxyl trans to the acetoxy group in the system (III) already established for delphinine.[3] There are now several pieces of evidence which prove this analogy of the partial structures beyond reasonable doubt.

Oxidation of oxonine [5] with chromium trioxide in pyridine gave a mixture of products from which a diketone (m.p. 238°) was obtained by chromatography on florisil in a yield of 5.4%. Calcd. for $C_{25}H_{35}O_{10}N \cdot 1/2\ H_2O$: C, 57.90; H, 7.01; O, 31.45; 4 OCH_3, 23.96%. Found: C, 57.68; H, 7.23: O, 32.18; OCH_3, 23.91%. Infrared (KBr): 3450, 1756, 1721, 1668 cm^{-1}. Ultraviolet: λ_{max}^{EtOH} 295 mμ, log = 1.95, $[\alpha]_D^{24}$ = -155° (ethanol).

We ascribe to this compound the structure IV. It is consequently analogous in the C-D ring system to α-oxodelphonone isomerized with base. The molecular rotation difference corresponding to the conversion of the C-D rings of oxonine to the C-D system of IV may be obtained from the rotations

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[4] R. Majima and H. Suginome, Ber. 58B, 2047 (1925).

[5] R. Majima, H. Suginome and H. Shimanuki, Ber. 65, 595 (1932).

of oxonitine, oxoaconitine, oxonine and IV. The result ($\Delta[\alpha] = -80^{\circ}$) agrees with the rotation change suffered by α-oxodelphonine on oxidation to α-oxodelphonone, followed by isomerization with base ($\Delta[\alpha]_D = -72^{\circ}$). Compound IV takes up 1 mole of lead tetraacetate to give in quantitative yield an amorphous keto acid formulated as V. (For the sake of brevity we shall use only one of the two possible alternatives in ring A.)

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The ultraviolet spectrum of V shows a shoulder at 230 mμ and a maximum at 255 mμ. The differential spectrum of V and desmethanol-aconinone [6] is identical with the spectrum of the seco acid from isomerized α-oxodelphonone which has the same characteristic but anomalous chromophore.[3]

We have been able to establish conclusively the analogy of II and III for aconitine and delphinine by a remarkable aromatization reaction. Oxonine takes up in acidic solution exactly 1 mole of periodic acid and the amorphous uncharacterized product VI gives, by heating to 70° in aqueous sodium hydroxide in a stream of oxygen, a phenol of the partial structure (VIII). This compound was isolated by chromatography on silicic acid in a yield of 10%, and remained amorphous. I.R.: 3550, 3420, 1670, 1620, 1585, 1505 cm^{-1}. U.V.: λ_{max}^{EtOH} 238, 283, 315 mμ, $\log \epsilon$ = 4.25, 3.83, 3.75; (alkaline EtOH): λ_{max} 256, 353 mμ, $\log \epsilon$ - 4.06, 4.18. These data are in agreement with a model acetophenone of the same substitution.

Methylation with diazomethane gave the methyl ether IX, m.p. 139°. This compound, in spite of precisely reproducible melting point and infrared spectrum, gave widely scattered combustion results for carbon. Calcd. for $C_{25}H_{33}O_8N$: H, 7.00; N, 2.95; 5 OCH_3, 32.67%. Found: H, 6.77; N, 2.67; OCH_3, 31.38%. I.R. ($CHCl_3$): 3660, 3400, 1670, 1605, 1505 cm^{-1}.

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[6] A. Lawson, J. Chem. Soc. 80 (1936).

U.V.: λ_{max}^{EtOH} 236.5, 279, 314 mμ, logϵ = 4.52, 4.08, 3.94.

Compound IX was then converted into a highly crystalline and correctly analyzing derivative (X) as follows. It was oxidized with chromium trioxide in acetic acid in quantitative yield to a diketone with no hydroxyl in the infrared. This compound, by vigorous reflux with methanolic HCl, lost the acetoxy group and eliminated the ring A methoxyl. The resulting base was reacetylated to X (m.p. 239°). Calcd. for $C_{24}H_{28}O_7N$: C, 65.21, H, 6.39; 4 OCH_3, 28.09%. Found: C, 65.31, 65.10; H, 6.17, 6.11; OCH_3, 26.00%. I.R.: No hydroxyl, 1685, 1652, 1605, 1505, 1465 cm^{-1}. U.V.: Identical with the sum of the desmethanolaconinone spectrum and the spectrum of IX.

The rationalization of this aromatization reaction involves a simple series of base catalyzed and oxidative steps proceeding from VI to VIII via VII. The loss of the aldehyde carbon in VII occurs at some stage in an oxidative reaction for which analogies can be found in the researches of Danilow.[7]

The proof of the correctness of our formulation is however not derived from mechanistic considerations, but from the fact that we have been able to modify the rigorously established [3] system III of delphinine in such a manner as to make it undergo the same reaction. The starting material was α-oxoisopyrodelphonine which by cleavage with 1 mole of periodic acid gave the crystalline secoaldehyde XI (m.p. 158°). Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; O, 25.03; 4 OCH_3, 27.74%. Found: C, 63.91; H, 7.31; O, 24.95; OCH_3, 27.66%.

Compound XI gave under identical conditions as those used with the aconitine derivative VI the phenol XIII (m.p. 123°) in a yield of

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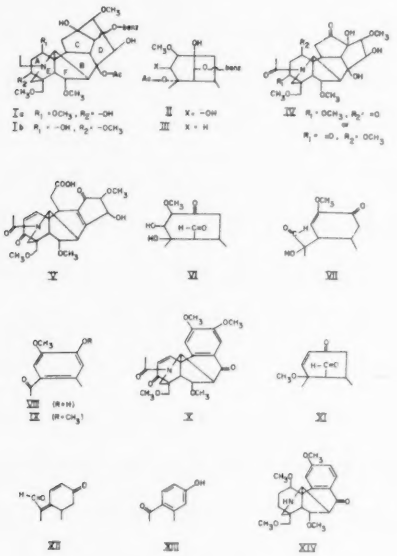
[7] S. Danilow, Ber. 60, 2390 (1927).

45%, presumably via the intermediate XII. Calcd. for $C_{22}H_{27}O_6N \cdot 1/2\ CH_3OH$: C, 64.73; H, 7.00; O, 24.91; N, 3.36; 3.5 OCH_3, 26.01%. Found: C, 64.93; H, 7.19; O, 24.28; N, 3.25; OCH_3, 25.95%. I.R.: 1697, 1653, 1612, 1582 cm^{-1}. U.V.: λ_{max}^{EtOH} 232, 285 mμ, log ε = 4.32, 4.24; (EtOH-NaOH): λ_{max} 246, 335 mμ, log ε = 4.18, 4.52.

The phenol XIII was methylated with diazomethane and the N-formyl group hydrolyzed. This gave a secondary base (m.p. 144°) formulated according to the structure deduced previously [3b] for delphinine as XIV. Calcd. for $C_{22}H_{29}O_5N$: C, 68.19; H, 7.54; 4 OCH_3, 32.04%. Found: C, 68.34; H, 7.52; OCH_3, 30.97%.



The relationship between the nitrogen atom and the acetoxy group became clear from the following transformations. Aconitine N-oxide (XV), m.p. 169° (dec.), was prepared by oxidation of aconitine (Ia) with peracetic

acid. The presence of the N-oxide functionality was established by reconversion to aconitine (Ia) by means of zinc dust in acetic acid and rearrangement with aqueous potassium chromate [8] to yield acetaldehyde. This latter finding confirms the presence of an N-ethyl group.[2] Pyrolysis [9] of aconitine N-oxide (XV) at 190° gave a very weakly basic compound (XVI), m.p. 255°, λ_{max}^{EtOH} 232 mμ, ε 18400; inflexion 255 mμ, ε 104000, λ_{210}, ε 10350; I.R. ($CHCl_3$) 3500, 3250 (OH); 1715 (benzoate); 1603 (nitrone, arom. C=C); 860 (trisubst. C=C?); calcd. for $C_{30}H_{39}O_{10}N$: C, 62.80; H, 6.85; N, 2.44; 3 act. H, 0.53; 4 OCH_3, 21.65%. Found: C, 62.83; H, 6.80; N, 2.38; act. H, 0.52; OCH_3, 21.91% which on hydrolysis was converted to an amorphous desbenzoyl compound (XVII), m.p. 192-194°, λ_{max}^{EtOH} 257 mμ, ε 8250; λ_{210}, ε 6800; I.R. ($CHCl_3$) 1603 cm^{-1} (nitrone). These findings demonstrate the loss of ethylene and acetic acid in the pyrolysis of XV but contrary to the pyrolysis of Ia no ketone function was produced. The spectral data of XVI and XVII are in fair agreement with those of XVIII, λ_{max}^{EtOH} 234 mμ, ε 8800; I.R. (neat) 1572 cm^{-1}. [10] Unfortunately no simple monomeric Δ^1-piperideine N-oxides are known.[11] Confirmatory evidence was provided by the N.M.R. spectrum (40 MC) of XVI which exhibited peaks (in $CDCl_3$) at 1018 c.p.s. (H on nitrone) and 1047 c.p.s. (vinyl hydrogen) (relative to 1000 c.p.s. for the aromatic proton of toluene). These critical bands were retained in the spectrum of deuterated XVI. The peak due to the nitrone proton is in good agreement with that of the simple nitrone XIX (1012 c.p.s.).[12] The N.M.R. spectrum furthermore

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[8] O. Diels and E. Fischer, Ber. 49, 1721 (1916); M. S. Fish, N. M. Johnson and E. C. Horning, J. Amer. Chem. Soc. 78, 3668 (1956).

[9] A. C. Cope, N. A. LeBel, H. H. Lee and W. R. Moore, J. Amer. Chem. Soc. 79, 4720 (1957); M. A. T. Rogers, J. Chem. Soc. 769 (1955).

[10] R. F. C. Brown, V. M. Clark and A. R. Todd, Proc. Chem. Soc. 97 (1957).

[11] J. Thesing and H. Mayer, Ber. 89, 2159 (1956).

[12] R. F. C. Brown, V. M. Clark and A. R. Todd, J. Chem. Soc. In press.

confirmed the absence of C-methyl groups in aconitine (Ia).

If it is assumed that the pentacyclic Δ^{17}-nitrone (XVI) originated from the initially produced hexacyclic hydroxylamine [9] the change can be rationalized by concerted fragmentation XX (arrows) and the molecular model of aconitine (Ia) clearly shows that the stringent stereoelectronic requirements [13] are met because N-C_{17}-C_7-C_8-OAc describe a plane. That no rearrangements had occurred in the pyrolysis was ascertained by reconversion of the nitrone (XVI) to aconitine (Ia). Treatment of XVI with zinc dust in hot acetic acid produced a mixture of secondary amines one of which was characterized by a N-nitroso derivative, m.p. 272° (dec.), I.R. (KBr) 3500 (OH); 1715 (acetate, benzoate); 1250 (acetate), calcd. for $C_{32}H_{42}O_{12}N_2$: C, 59.40; H, 6.55; N, 4.33. Found: C, 59.15; H, 6.59; N, 4.15. Ethylation of the mixture of secondary amines with ethyl iodide gave aconitine (Ia) in 28% yield (based on nitrone (XVI)) identified by m.p., mixed m.p., I.R. spectrum and analysis with an authentic sample. The Δ^{17}-nitrone (XVI) has thus undergone acid catalyzed cyclization to a hexacyclic acetoxhydroxylamine which in turn was reduced by zinc to the corresponding secondary amine. The scale model of XVI illustrates the spatial proximity of the C=N and the C=C double bonds and the change is analogous to that proposed for the biogenesis of lycoctonine and delpheline.[14]

The facile cyclization of the nitrone was verified by the following additional transformations. Treatment of the desbenzoyl-nitrone XVII with perchloric acid in methanol gave a crystalline

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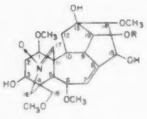
[13] S. Archer, T. R. Lewis and B. Zenitz, J. Amer. Chem. Soc. 80, 958 (1958); A. T. Bottini, C. A. Grob and E. Schumacher, Chem. & Ind. 757 (1958).

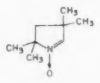
[14] R. C. Cookson and M. E. Trevett, J. Chem. Soc. 3121 (1956); Z. Valenta and K. Wiesner, Chem. & Ind. 354 (1956).

perchlorate (XXI), m.p. 250° (dec.), no U.V., λ_{216}, ϵ 135; no nitrone band in the I.R. which exhibited a strongly positive TTC test [15] characteristic of hydroxylamines; calcd. for $C_{24}H_{39}O_{10}N \cdot HClO_4$: C, 47.88; H, 6.70; N, 2.33; 5 OCH_3, 25.78%. Found: C, 48.05; H, 7.02; N, 2.22; OCH_3, 25.90%. Furthermore the reaction of XVII with perchloric acid in ethanol produced a different salt (XXII), m.p. 250° (dec.), λ_{210}^{EtOH}, ϵ 138; calcd. for $C_{25}H_{41}O_{10}N \cdot HClO_4$: C, 48.73; H, 6.87; N, 2.27. Found: C, 48.25; H, 6.75; N, 2.30.

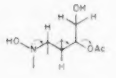


XVI R = BENZOYL
XVII R = H

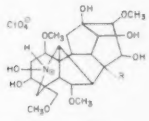
XVIII



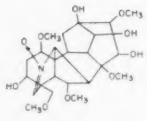
XIX



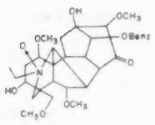
XX



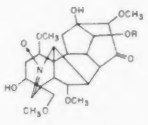
XXI R = -OMe
XXII R = -OEt



XXIII



XXIV



XXV R = BENZOYL
XXVI R = H

Aerial oxidation of the C_{24} hydroxylamine perchlorate (XXI) in aqueous ammonia in the presence of cupric ion gave the crystalline Δ^{16}-nitrone (XXIII), m.p. 183-185°, λ_{max}^{EtOH} 245 mμ, ϵ 7420; λ_{216}, ϵ 2580;

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[15] G. A. Snow, J. Chem. Soc. 2588 (1954).

I.R. ($CHCl_3$) 1613 (nitrone). The relationship of this new nitrone (XXIII) to the hydroxylamine (XXI) was established by reduction of XXIII to XXI with sodium borohydride. Similarly, treatment of the benzoylnitrone (XVI) successively with methanolic perchloric acid, with air, ammonia and cupric ion, and with aqueous sodium hydroxide gave the Δ^{16}-nitrone XXIII.

If our views on the pyrolysis of aconitine N-oxide (XV) to the Δ^{17}-nitrone (XVI) are correct, the pyrolysis of pyroaconitine N-oxide (XXIV) should lead to a hexacyclic hydroxylamine. This assumption was fully confirmed by experiment. Pyroaconitine N-oxide (XXIV), m.p. 159-164° (dec.) on pyrolysis gave an amorphous hydroxylamine, pos. TTC test, no nitrone bands in the I.R., which was oxidized as above to a crystalline Δ^{16}-nitrone (XXV), m.p. 230-232°, λ_{max}^{EtOH} 234 mμ, ϵ18500, inflexion at 255 mμ, ϵ8800, λ_{210}, ϵ7050, I.R. ($CHCl_3$) 1604 (nitrone), 1725 cm^{-1} (benzoate); calcd. for $C_{30}H_{34}O_{10}N$: C, 63.03; H, 6.53; N, 2.45. Found: C, 62.94; H, 6.60; N, 2.07. Base hydrolysis of XXV gave the Δ^{16}-desbenzoylnitrone (XXVI), m.p. 270-272°, λ_{max}^{EtOH} 249 mμ, ϵ8060, λ_{210}, ϵ2200; I.R. (Nujol) 1625 cm^{-1} (nitrone).

There is no direct evidence for the locations of the primary methoxyl group and the methoxyl in ring F. However, it is clear that there are only three positions (C_5, C_6, C_{18}) vacant for the two groups and the arrangement chosen in I coincides with the situation for which there is experimental evidence in delphinine chemistry [3b] and crystallographic evidence in lycoctonine.

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[16] M. Przybylska and L. Marion, Canad. J. Chem. 34, 185 (1956).

The New Brunswick group is indebted to Pfizer of Canada Ltd. and to the Schering Corporation for grants-in-aid, and M. G. to the NRC for a postdoctoral fellowship. The M. I. T. group wishes to acknowledge generous financial support by Chas. Pfizer and Co. Inc. and R. F. C. B. thanks the Sloan Foundation for a foreign postdoctoral fellowship.

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ABSTRACTS OF SOME OF THE PAPERS TO BE PUBLISHED IN FUTURE ISSUES OF TETRAHEDRON

DIENON-PHENOL-UMLAGERUNG VON CHINOLEN—II

BEITRAG ZUR KLÄRUNG DES REAKTIONSMECHANISMUS

W. METLESICS, F. WESSELY und H. BUDZIKIEWICZ
Chemischen Institut der Universität Wien

(*Received* 26 *December* 1958)

Zusammenfassung—Es werden Umlagerungen von *o*- und *p*-Chinolacetaten und von *p*-Chinolen unter den Bedingungen der Thiele'schen Reaktion beschrieben. Zur Klärung des Reaktionsmechanismus wurden auch Umlagerungen in Diacetylsulfid durchgeführt.

Der Dualismus im Reaktionsverhalten zwischen *p*-Chinolen und *p*-Chinolacetaten wird ausführlich diskutiert.

Die Ergebnisse der Säureeinwirkung auf *p*-Toluchinol und dessen Acetat sind mit unseren Vorstellungen über den Ablauf der anderen hier behandelten Reaktionen im Einklang.

Abstract—Rearrangements of *o*- and *p*-quinol-acetates and of *p*-quinols under conditions of the Thiele-reaction are described. To investigate the mechanism of these reactions rearrangements have also been carried out in diacetyl-sulfide.

The differences between the reactions of *p*-quinols and *p*-quinol-acetates are being discussed in some detail.

The results of action of acids upon *p*-toluquinol and its acetate are in accordance with our conceptions on the course of other reactions mentioned in this paper.

STEREOCHEMISTRY OF THE PRIMARY CARBON—X

STEREOCHEMICAL CONFIGURATIONS OF SOME OPTICALLY ACTIVE DEUTERIUM COMPOUNDS

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Chemistry Department, University of California, Berkeley 4, California

Abstract—The *iso*bornyloxymagnesium halide reduction of the appropriate deutero-aldehyde yields benzyl-α-*d* alcohol and 1-butanol-1-*d* having the same configuration and about the same level of optical purity. Arguments are presented that these alcohols are close to optical purity. The relative configurations of each alcohol were established by converting each to 1-phenylbutane-1-*d* using reactions of known or presumed stereochemistry. The rotations and configurations of 18 optically active deuterium compounds are summarized.

HETEROCYCLIC FLUORINE COMPOUNDS—III

MONOFLUOROXANTHONES

F. L. ALLEN, P. KOCH and H. SUSCHITZKY
The Department of Chemistry and Biology, West Ham College of Technology, London, E.15,
and
The Department of Chemistry and Applied Chemistry, Royal Technical College, Salford, Lancs

(*Received* 25 *November* 1958)

Abstract—The four monofluoroxanthones substituted in the benzene ring have been prepared by two different routes, namely by cyclisation of the appropriate carboxyfluorodiphenyl ether and by a Balz–Schiemann reaction with the corresponding aminoxanthone.

ASPECTS OF STEREOCHEMISTRY—II*

INTRAMOLECULAR HYDROGEN BONDING IN SOME MONOHYDROXY DERIVATIVES OF TETRAHYDROFURAN, TETRAHYDROPYRAN AND 1:3-DIOXAN

S. A. BARKER, J. S. BRIMACOMBE, A. B. FOSTER, D. H. WHIFFEN and G. ZWEIFEL
Chemistry Department, The Univeristy, Birmingham

(*Received* 19 *January* 1959)

Abstract—The extent of intramolecular hydrogen bonding between hydroxyl groups and ring oxygens, as determined by infra-red spectroscopy in the hydroxyl stretching region, in a series of monohydroxy derivatives of tetrahydropyran, tetrahydrofuran and 1:3-dioxan provides direct experimental evidence for the stabilities of different conformations of certain of the alcohols. The synthesis of tetrahydropyran-3-ol is described and the mechanism of the reaction of perbenzoic acid with glycals is discussed.

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Papers to be published in future issues of "Tetrahedron"

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H.J.E. LOWENTHAL : Selective reactions and modification of functional groups in steroid chemistry.

Gj. STEFANOVIĆ, M. PAVIČIĆ - WOSS, Lj. LORENC and M. Lj. MIHAILOVIĆ : Some applications of the Pfitzinger reaction. Condensation of isatin with diketones.

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A.J. BIRCH and D. NASIPURI : Reaction mecha··sms in reductions by metal-ammonia solutions.

F. KORTE, J. FALBE und A. ZSCHOCKE : α-Hydroxyalkyliden-lacton-Umlagerung -IX. Synthese des D,L-Iridomyrmecins und verwandter bicyclischer Lactone.

K.J. CLARK, G.I. FRAY, R.H. JAEGER and Sir ROBERT ROBINSON : Synthesis of D- and L-isoiridomyrmecin and related compounds.

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T.L.V. ULBRICHT : Synthesis of pyrimidine-lithium compounds.

N.R. AYYANGAR, B.S. JOSHI and K. VENKATARAMAN : Anthraquinone and anthrone series - XXIII. The non-identity of 1:3:8-trihydroxy-2-hydroxymethylanthraquinone with versicolorin and a synthesis of damnacanthol and damnacanthal.

F.L. ALLEN, P. KOCH and H. SUSCHITZKY : Heterocyclic fluorine compounds-III. Monofluoro-xanthones.

W. METLESICS, F. WESSELY und H. BUDZIKIEWICZ : Dienon- Phenol- Umlagerung von Chinolen - II. Beitrag zur Klärung des Reaktionsmechanismus.

E. CLAR : Asymmetric annellation effects - II.

E. CLAR, C.T. IRONSIDE and M. ZANDER : Asymmetric and symmetric annellation effects - III. Benzocoronenes.

A. STREITWIESER, Jr.,J.R. WOLFE, Jr. and W.D. SCHAEFFER : Stereochemistry of the primary carbon - X. Stereochemical configurations of some optically active deuterium compounds.

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S.A. BARKER, J.S. BRIMACOMBE, A.B. FOSTER, D.H. WHIFFEN and G. ZWEIFEL: Aspects of stereochemistry - II. Intramolecular hydrogen bonding in some monohydroxy derivatives of tetrahydrofuran, tetrahydropyran and 1:3-dioxan.

A.K. BARUA and S. PATTABI RAMAN : Triterpenoids - X. The constitution of albigenic acid - a new triterpenoid sapogenin from Albizzia lebbeck Benth.

P.K. GROVER and T.R. SESHADRI : Constitution of pinastric acid.

G. GAUDIANO, A. QUILICO and A. RICCA : Poly-isoxazoles.

1959

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THE BIOSYNTHESIS OF CITRONELLAL AND OF CINEOLE IN EUCALYPTUS

A.J.Birch, D.Boulter, R.I.Fryer, (Mrs) P.J.Thomson and J.L.Willis.

Manchester University, Liverpool University,
and Museum of Applied Arts and Sciences, Sydney.

1959

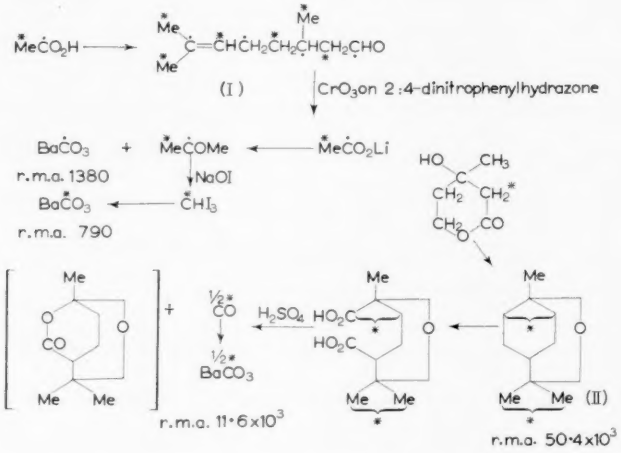
(Received 12 March 1959)

LITTLE work has been done on the biosynthesis of plant terpenes, and in order to investigate the experimental techniques of incorporation we have fed $Me^{14}CO_2H$ into citronellal in Eucalyptus citriodora Hook and 2-^{14}C-mevalonic lactone into cineole in E.globulus.Lab. Terminal branchlets (total weight about 50 g) were allowed to absorb by transpiration acqueous solutions (about 30 cc) containing the labelled precursor, assisted if necessary by a current of warm air. The oils were obtained by steam-distillation (cohobation technique), citronellal being isolated as its 2:4-dinitrophenylhydrazone, and cineole as the resorcinol complex. Dilution with inactive material (about 200 mg) assisted purification and provided sufficient material for degradation. The incorporations were small, but sufficient for further investigation.

The pattern expected for citronellal is (I) and with $Me^{14}CO_2H$ as precursor the activity should be zero if no randomisation occurs. The result shown, based on Kuhn-Roth oxidation, supports the expected distribution although randomisation is considerable, the accuracy being good in view of rather low activities [Found for the whole molecule: r.m.a. 11 x 10^3; calc. from the sum of the r.m.a. contributions based on

(I) and the results of the Kuhn-Roth oxidation: r.m.a. 10 x 10^3]. The randomisation may occur through formation of $^{14}CO_2$ and photosynthesis.

The pattern expected for cineole from 2-^{14}C-mevalonic lactone is (II) and is supported by the degradation shown: little if any randomisation appears to have occurred. The degradation assumes that the isotope effect in the oxidation to cineolic acid is small.



Clearly, this technique can be used for other leaf terpenes, especially with mevalonic lactone. While this work was in progress Stanley [1] showed that mevalonic acid could be incorporated into α-pinene, but did not degrade the product.

We are indebted to Dr. Herchel Smith for assistance with the tracer measurements, to the Rockefeller Foundation and Chas. Pfizer and Co. Inc. for financial assistance, and to Imperial Chemical Industries Limited for the loan of tracer equipment.

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[1] R. G. Stanley, Nature, Lond., 182, 738 (1958).

Tetrahedron Letters, No. 3, pp. 3-6, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

THE SYNTHESIS OF CYCLOÖCTADECANONAENE, A NEW AROMATIC SYSTEM *

Franz Sondheimer and Reuven Wolovsky

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(Received 16 March 1959)

THE synthesis and possible aromatic properties of monocyclic hydrocarbons formally containing alternating single and double bonds (vinylogs of benzene) have often been discussed.[1] Nevertheless the only member of this series known up to now besides benzene itself is cycloöctatetraene, despite numerous synthetic attempts to prepare other members. We now describe the synthesis of cycloöctadecanonaene (II) (for brevity named CON in this communication), the first cyclic polyene after benzene which might be expected to exhibit aromatic properties since (a) it can probably take up a planar or near planar configuration and (b) it

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* First presented at a Seminar at Harvard University, Nov. 21, 1958. This is Part IX of the Series, "Unsaturated Macrocyclic Compounds"; for Part VIII, see F. Sondheimer, Y. Amiel and R. Wolovsky, J. Amer. Chem. Soc. In press.

[1] Inter al. K. Mislow, J. Chem. Phys. 20, 1489 (1952); W. Baker and J.F.W. McOmie in Progress in Organic Chemistry (Edited by J.W. Cook) Vol. 3, p. 44. Butterworths Scientific Publications, London (1955); W. Baker in Perspectives in Organic Chemistry (Edited by Sir A. Todd) p. 28. Interscience, New York (1956).

contains $(4n + 2)$ π -electrons.[2]

We have recently reported two different syntheses of cycloöctadeca-1,7,13-(cis)-triene-3,9,15-(trans)-triene-5,11,17-triyne (I).[3,4] This compound on being partially hydrogenated in benzene over a "Lindlar" palladium catalyst[5] directly yielded a solution with three new ultra-violet maxima at 378, 415 and 456 mμ. Chromatograpny on alumina gave first unchanged I and then ca. 30% of CON (II) as long brown-red needles from chloroform (yellow-green solution in benzene), empirical formula $C_{18}H_{18}$ (found C, 91.76; H, 7.67), λ isooctane 278,369, 408 and 448 mμ (ϵ = 8100, 303,000, 7500 and 21,800, $\lambda_{max.}^{benzene}$ 378, 415 and 456 mμ (ϵ = 297,000, 8700 and 28,400). In the infra-red (KBr) CON showed bands at 3.32 (m), 6.33 (w), 7.63(s), 7.93(m), 9.72(w), 10.36(m), 10.72(s), 11.86(s) and 13.16(w) μ. Full hydrogenation in diozane over platinum smoothly yielded cycloöctadecane, m.p. and mixed m.p. 72-73°.

The ultra-violet spectrum of CON indicates all the double bonds to be part of one chromophoric system (cf. the linear nonaene analog III, which has the highest wavelength maximum at 456 mμ, in benzene).[6]

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[2] E. Hückel, Z. Physik 70, 204 (1931); Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin (1938).

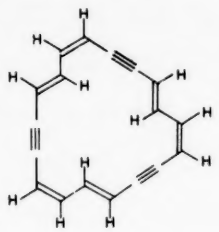
[3] F. Sondheimer and R. Wolovsky, J. Amer. Chem. Soc. In press.

[4] F. Sondheimer, Y. Amiel and Y. Gaoni, J. Amer. Chem. Soc. In press.

[5] H. Lindlar, Helv. Chim. Acta 35, 446 (1952).

[6] F. Bohlmann, Ber. 85, 386 (1952).

CON is therefore comparatively planar and it follows that the hydrogenation of I has resulted in trans-addition of hydrogen, since the usual cis-addition would have given a nonaene which cannot be planar.



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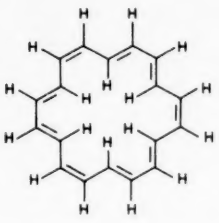
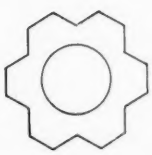


II

Me-(CH=CH)$_9$-Me

III



II a

This view is substantiated by X-ray work now being carried out at this Institute by J. Bregman and G.M.J. Schmidt (to be published elsewhere); preliminary results based on the crystallographic constants suggest that CON is a near-planar molecule approximating to a centrosymmetric configuration.

CON contains a continuous molecular orbital and may be written as (IIa). It is an 18 π-electron system in which all the carbon-carbon bonds may well be equivalent and equal in length, as in benzene.*

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* We hope that a full X-ray structure analysis which is in progress will throw light on this important question.

CON shows definite aromatic character, being strikingly more stable than the acyclic analog III which decomposes very rapidly at room temperature.[6] Thus CON can be sublimed at 120-130° (0.5 mm) and on a Kofler block it appears to remain unchanged up to 230°.* However CON is not as stable as a classical benzenoid system (e.g. it gradually decomposes on being allowed to stand in light and air over the course of several weeks) and this may be a reflection of the interaction of the central hydrogen atoms.

Since the hexaene-triyne I is available in ca. 3% yield from 1,5-hexadiyne by a simple two-step route,[3] it is possible to prepare reasonable quantities of CON without undue difficulty. Various problems regarding the planarity and aromaticity of CON are now being investigated.

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* At this point a non-reversible colour-change takes place (the needles becoming light yellow without change of crystal shape), the nature of which is being studied.

Tetrahedron Letters, No. 3, pp. 7-8, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE CONSTITUTION OF HYPOGLYCIN B

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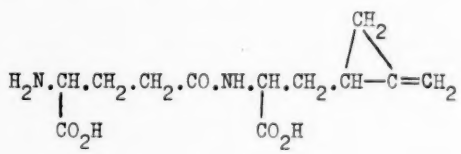
Chemistry Dept., University College, Swansea

(Received 23 March 1959)

1959

IN a recent publication [1] there is evidence supporting the formulation of hypoglycin B[2] as the dipeptide γ-L-glutamyl-α-amino-β-(2-methylene-cyclopropyl) propionic acid (I). This is based on hydrolysis experiments on the peptide and its 2,4-dinitrophenyl-derivative, together with the indication by Van Slyke amino-nitrogen and carboxyl determinations that the glutamic acid residue is attached by a γ-link. We have been led independently, by similar evidence, to the same conclusion concerning the structure of hypoglycin B. In addition, we have confirmed this structure by synthesis, using a procedure which, as model experiments have shown, leads to a γ-glutamyl peptide.[3]



I

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[1] A. Johl and W.G. Stoll, Helv. Chim.Acta 42, 156 (1959)

[2] C.H. Hassall and K. Reyle, Biochem.J. 60, 334 (1955)

[3] G. Amiard, R. Heymes and L. Velluz, Bull.Soc.Chim.Fr. 698 (1956).

The methyl ester of (+) hypoglycin A condensed with the triethylamine salt of N-trityl-L-glutamic acid in the presence of dicyclohexyl-carbodiimide. The product was hydrolysed with 0.2 N-solium hydroxide (3 hr, 40°), then detritylated with 50% acetic acid (3 min, 100°) to give the dipeptide I which is identical with hypoglycin B. The synthetic product has $[\alpha]_D^{19}+9° \pm 2°$; D.N.P. derivative, m.p. and mixed m.p. with D.N.P. - hypoglycin B, 163-166°C; the infra-red spectra of the natural and synthetic compounds and their D.N.P. derivatives are identical.

Tetrahedron Letters, No. 3, pp. 9-10, 1959. Pergamon Press Ltd. Printed in Great Britain.

LITHIUM TRIETHOXYALUMINOHYDRIDE AS A CONVENIENT REAGENT FOR THE CONVERSION OF NITRILES TO ALDEHYDES

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Purdue University, Lafayette, Indiana

(Received 30 March 1959)

The conversion of nitriles to aldehydes is a synthetic route of considerable importance.[1] Both the Stephen procedure and the partial reduction with lithium aluminum hydride are usually satisfactory for the conversion of aromatic nitriles, but are less than satisfactory for aliphatic nitriles.[1,2,3] Our recent success in utilizing alkoxy substituted lithium aluminohydrides for the conversion of acid chlorides[4] and of N,N-dimethylamides[5] to aldehydes encouraged us to examine the utility of these reagents for the reduction of nitriles to aldehydes.

Lithium triethoxyaluminohydride is conveniently synthesized *in situ* by adding either 3.00 moles of ethanol or 1.50 moles of ethyl acetate to one mole of lithium aluminum hydride in ether solution (1.3 M) at 0°. To this solution, maintained at 0°, one mole of the nitrile is added. After one hour at 0°, one-half volume of methanol is added to destroy residual unreacted hydride and give a homogeneous solution. The aldehyde yield is based on an analysis of an aliquot of the solution with 2,4-dinitrophenylhydrazine. The results are summarized in Table 1.

From these results, it appears that aliphatic nitriles can be converted to aldehydes by this procedure in yields of 70-80%, and aromatic nitriles, in yields of 80-90%. Consequently, the reduction of nitriles by lithium triethoxyaluminohydride promises to provide a synthetic route from nitrile to aldehyde of some generality. We are continuing to explore the full scope of this reduction.

[1] E. Mosettig, Organic Reactions Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 218-257.
[2] C. J. Claus and J. L. Morgenthau, Jr., J. Amer. Chem. Soc. 73, 5005 (1951).
[3] S. Pietra and C. Trinchera, Gazz. chim. ital. 85, 1705 (1955).
[4] H. C. Brown and R. F. McFarlin, J. Amer. Chem. Soc. 80, 5372 (1958); H. C. Brown and B. C. Subba Rao, ibid. 80, 5377 (1958).
[5] H. C. Brown and A. Tsukamoto, ibid. 81, 502 (1959).

TABLE 1. YIELD OF ALDEHYDES IN THE REDUCTION OF NITRILES BY LITHIUM TRIETHOXYALUMINOHYDRIDE

Nitrile	Aldehyde yield, %
n-Butyronitrile	68
n-Capronitrile	69
Isobutyronitrile	81
Cyclopropanecarbonitrile	69
Cyclohexanecarbonitrile	76
Benzonitrile	96
o-Tolunitrile	87
α-Naphthonitrile	80
o-Chlorobenzonitrile	87
p-Chlorobenzonitrile	92
Cinnamonitrile	61

Recently, it was reported that sodium triethoxyaluminohydride, prepared from the reaction of sodium hydride with aluminum ethoxide, successfully reduced aromatic nitriles to aldehydes, but is unsatisfactory for aliphatic nitriles.[6] We are unable to account at this time for this apparent major difference in the applicability of the sodium and lithium reagents.

Acknowledgement—This investigation was made possible by Contract DA-33-008-ORd-992 supported by the Office of Ordnance Research, U. S. Army. This assistance is gratefully acknowledged.

[6] G. Hesse and R. Schrödel, Ann. 607, 24 (1957).

Tetrahedron Letters, No. 3, pp. 11-14, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF DELPHININE

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Organic Chemistry Laboratory, University of New Brunswick, Canada

(Received 1 April 1959)

Some time ago we deduced the structure and substitution of the C-D ring system of delphinine.[1,2] At the same time we have also shown that the considerable body of evidence accumulated by Jacobs [3] can be fitted extremely well into the complete structures I and II. Besides these structures, we have also discussed two structures with a rearranged ring B to account for the positive outcome of the Hofmann degradation [4] reported by Jacobs and Schneider.

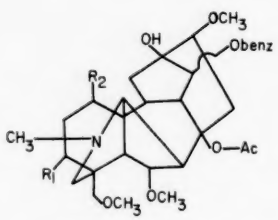
We now wish to present evidence that structure I is the correct representation of delphinine. Delphonine formed a crystalline methiodide which melted at 208-211°. Calc. for $C_{25}H_{42}O_7NI$: C, 50.42; H, 7.11; I, 21.33; 4 OCH_3, 20.77%. Found: C, 50.73: H, 7.02; I, 21.25; OCH_3, 20.44%. The methiodide was converted into the methohydroxide on a column of amberlite IRA-400 and the methohydroxide was heated with 10% aqueous sodium hydroxide until most of the water evaporated. A three-fold countercurrent distribution of the resulting bases between buffer pH 5.8 and chloroform resulted in the isolation (in a 5% yield) of compound III which was further purified by sublimation and recrystallized to a melting point of 153°. Calc. for $C_{23}H_{37}O_5N$: C, 67.78; H, 9.15; 3 OCH_3, 22.85%. Found: C, 67.52, 67.52; H, 9.30, 9.02; OCH_3, 22.48%.

The infrared spectrum of III shows a strong ketonic peak at 1707 cm^{-1} and no peak in the hydroxyl region. The presence of two keto groups was corroborated by the preparation of a bis 2,4-dinitrophenylhydrazone which was microcrystalline and decomposed at 157°. Calc. for $C_{35}H_{45}O_{11}N_9$: C, 54.74; H, 5.90; N, 16.41; 3 OCH_3, 12.12%. Found: C, 53.70; H, 5.73: N, 16.45; OCH_3, 12.37, 10.22%.

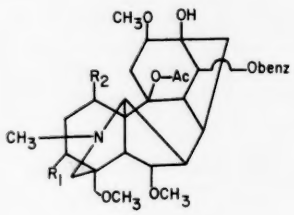
The N.M.R. spectrum of compound III which was recorded and interpreted by Mr. J. Atkinson (Chemistry Department, M.I.T., Cambridge, Mass.) is in agreement with the presence of a disubstituted double bond.

The formation of III is easily rationalized by a 1-3 cleavage, followed by the elimination of the ring D methoxyl, a reverse aldole reaction and cleavage of a vinylogous β-keto aldehyde. Thus, the supposed Hofmann degradation of delphinine is explained and it is conceivable that compound III is identical with the "methine" described by Schneider.[4] Treatment of a very small amount of compound III with bromine followed by alkali gave an impure mixture which, nevertheless, exhibited an ultraviolet spectrum both in acidic and basic solution strongly resembling a brominated γ-tropolone.[5]

We have postulated in our previous work that the pyro-isopyro change of delphinine derivatives is an allylic rearrangement of a methoxyl [2]



I $R_2 = OCH_3$, $R_1 = H$
$R_2 = H$, $R_1 = OCH_3$



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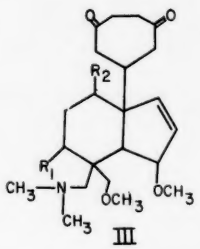

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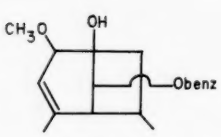

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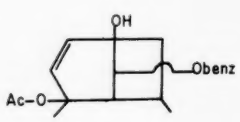

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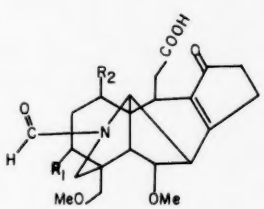
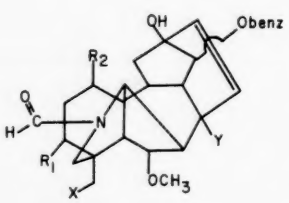
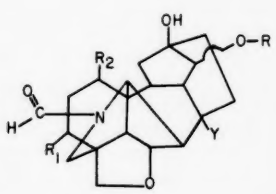


X



XI (X, Y = Cl)
XII (X, Y = OH)
XIII ($X = CO_2H$, Y = OH)
XV ($X, Y = OCD_3$)



XIV ($Y = OCH_3$, R = hexahydrobenzoyl)
XVI ($Y = OCD_3$, R = hexahydrobenzoyl)

The following evidence was assembled in support of this assumption:

(a) The identity of the skeletal structure of delphinine and isopyro-delphinine derivatives was proved.
(b) It was shown that delphinine and isopyrodelphinine derivatives differ in the site of attachment of one methoxyl.
(c) It was shown that one methoxyl is exchanged when the pyro-isopyro rearrangement is carried out in radioactive methanol.

However, no direct proof was provided that the same methoxyl which is exchanged in the rearrangement eliminates in the formation of the secoacid X.

1959

We have now shown that this prediction is correct. Pyrooxodelphinine IV was rearranged in glacial acetic acid in the presence of a small amount of p-toluene sulphonic acid to the acetoxyisopyro compound V (m.p. 305°) in quantitative yield. Calc. for $C_{32}H_{39}O_9N$; C, 66.07; H, 6.76; 3 OCH_3, 16.00%. Found: C, 66.35; H, 6.75; OCH_3, 15.51%.

Compound V was converted into the octahydroderivative VI (m.p. 229°) by hydrogenation with platinum oxide in glacial acetic acid. Calc. for $C_{32}H_{47}O_9N$: C, 65.17; H, 8.03; 3 OCH_3, 15.82%. Found: C, 65.45; H, 7.97; OCH_3, 15.96%. Compound VI was then hydrolysed to the corresponding triol VII which melted at 239°. Calc. for $C_{23}H_{35}O_7N$: C, 63.14; H, 8.06; 3 OCH_3, 21.28%. Found: C, 63.29; H, 8.04; OCH_3, 20.87%. Compound VII was then converted into the crystalline acid X (m.p. 138°) by oxidation with chromium trioxide, esterification of the resulting seco keto acid with diazomethane, treatment of the keto ester with hot methanolic sodium methoxide and alkaline hydrolysis. The identical acid X has previously [2] been obtained by a completely analogous series starting from isopyrooxodelphinine. This shows conclusively that, as predicted by our scheme, the methoxyl which is exchanged in the pyro-isopyro reaction is also the one which eliminates in the formation of compound X.

We have further verified our explanation [2] of the demethylation experiments of Jacobs.[3] This author has shown that treatment of isopyrooxodelphinine with methanolic hydrochloric acid will result in the replacement of two methoxyls by chlorine and give a dichloride which we now formulate as XI. Treatment of XI with methanol gives back isopyrooxodelphinine. The chlorines of XI may also be replaced by hydroxyls to give the triol XII. This last compound may be oxidized to the hydroxy acid XIII.

It is clear that the tertiary hydroxyl displaced by chlorine must be the one engaged in the pyro-isopyro rearrangement. The fact that the same dichloride XI is obtained both from pyro- and isopyrooxodelphinine is sufficient proof of this assumption.

Jacobs has further shown that octahydro-isopyrooxodelphinine on treatment with aqueous zinc chloride gives a dimethoxy ether formulated

by us as XIV. Jacobs believed that the internal ether formation took place between the same two methoxyls which undergo easy displacement by chlorine. While he has undoubtedly shown that the primary methoxyl is involved in the internal ether, he provided no experimental evidence for the identity of the second methoxy group.

We have now shown conclusively that in agreement with our formulation of XIV one of the two methoxyls which gave rise to the internal ether is not identical with either of the two methoxyls displaced by chlorine in compound XI. The dichloride XI was converted by refluxing with CD_3-OH into labelled isopyrooxodelphinine XV. This compound showed the same melting point (285°) and practically the same infrared spectrum as isopyrooxodelphinine; the two materials gave no melting point depression. Calc. for $C_{31}H_{33}D_6O_8N$: 15.4 atom % xss D. Found: 13.0 atom % xss D.

The labelled isopyrooxodelphinine XV was then converted into the cyclic ether XVI which had the same melting point (266°) and practically the same infrared spectrum as compound XIV but retained one deuterated methoxyl. Calc. for $C_{29}H_{38}D_3O_7N$: 2 OCH_3, 11.97%; 7.3 atom % xss D. Found: OCH_3, 10.71%; 6.83 atom % xss D.

If we compare the recently deduced [6] structure of aconitine with the delphinine formula which we have conclusively established in this Communication, it appears exceedingly probable that aconitine is a dihydroxy delphinine. Attempts at direct correlation of these two important alkaloids are in progress.

We are indebted to the National Research Council, Ottawa for postdoctoral fellowships to F.B. and M.G. and to the Research Corporation, New York for a grant which enabled us to undertake the isolation of delphinine on a large scale.

1. K. Wiesner, F. Bickelhaupt and Z. Valenta, Tetrahedron 4, 418 (1958).
2. K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia (in press).
3. W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc. 76, 161 (1954).
4. W. A. Jacobs and S. W. Pelletier, J. Org. Chem. 22, 1428 (1957); W. Schneider, Archiv. pharm. 283, 86, 281 (1950).
5. T. Nozoe, T. Mukai, Y. Ikegami and T. Toda, Chem. and Ind. 66 (1955).
6. K. Wiesner, M. Götz, D. L. Simmons and L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters No. 2, 15 (1959).

Tetrahedron Letters, No. 3, pp. 15-18, 1959. Pergamon Press Ltd.
Printed in Great Britain.

1959

AROMADENDRENE AND VIRIDIFLOROL

A. J. Birch, J. Grimshaw and R. N. Speake

University of Manchester

R. M. Gascoigne and R. O. Hellyer

University of New South Wales

(Received 3 April 1959)

FORMULA (I) advanced [1] as a possibility for aromadendrene is more likely to be correct than the alternative with the cyclopropane ring terminating at the 6-position since dehydrogenation gives only S-guaiazulene. Ozonolysis of aromadendrene from Metrosideros scandens [2] gave α-apoaromadendrone, isomerised by alkali to the well known apoaromadendrone, and it was assumed that this hydrocarbon and the aromadendrene from Eucalyptus nova-anglica and other sources were identical and therefore had a trans-9,10-ring junction. Failure to obtain α-apoaromadendrone from the latter hydrocarbon in the Manchester and several other laboratories indicates

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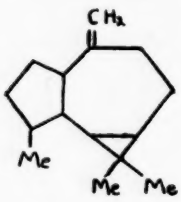
[1] A.J. Birch and F.N. Lahey, Aust. J. Chem. 6, 379 (1953).

[2] A.J.Birch, J. Chem. Soc. 715 (1953).

that the M. scandens hydrocarbon (α-aromadendrene) is a stereoisomer with a trans-9,10-ring junction and that the authentic aromadendrene has the cis-ring junction.

Globulol has been shown [3] to be a stereoisomer of (II) related stereochemically to aromadendrene; we have found that viridiflorol [4] (identical with himbaccol [5])



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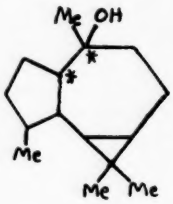

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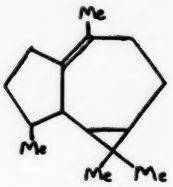

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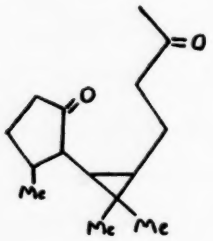

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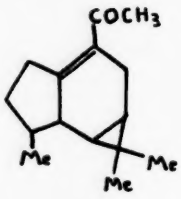

V

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[3] A. Blumann, A.R.H. Cole, K.J.L. Thiaberg and D.E. White, Chem. and Ind. 1426, (1954).

[4] T.G.H. Jones and W.L. Haenke, J. Roy. Soc. Queensland 49, 95 (1938).

[5] A.J. Birch and K.M.C. Mostyn, Aust. J. Chem. 8, 550 (1955).

yields some α-aromadendrene on pyrolysis of its phenylurethane. The product ($C=CH_2$ bands at 3085; 1638; 890 cm^{-1}) on ozonolysis gave α-apoaromadendrone, m.p. 71-72°; $[\alpha]_D^{23}$ -14°, isomerised by base to apoaromadendrone, m.p. and mixed m.p. 83-84°; $[\alpha]_D^{23}$ +3°. Dehydration of viridiflorol by alcoholic sulphuric acid produced some ledene identified as the glycol,[6] m.p. and mixed m.p. 150-151°; $[\alpha]_D^{20}$ -15.5°. Lead tetraacetate fission of the glycol gave a diketone (IV) (carbonyl bands at 1740 and 1715 cm^{-1}, bis-2,4-dinitrophenylhydrazone, m.p. 115-118°) also obtained by chromic acid oxidation of viridiflorol. The diketone was cyclised by alkali to an αβ-unsaturated ketone probably (V) (acetyl ν_{max} 1356 cm^{-1}) contaminated with its βγ-isomer ($\lambda_{max.}^{alc.}$ 241mμ; ν_{max} 1710 and 1688 cm^{-1}). This supports the formula (III) advanced for ledene[7] and the suggestion that ledol and palustrol [8] are probably stereoisomers of (II).[7] Therefore in all probability ledol, palustrol,

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[6] N.P. Kyrialov, Zhur. Obshcheĭ Khim. 21, 2077 (1951); Chem. Abs. 46, 6633 (1952)

[7] L. Dolejs, F. Sorm and M. Soucek, Chem. and Ind. 160 (1959).

[8] N.P. Kyrialov, Zhur. Obshcheĭ Khim. 24, 1271 (1954); Chem. Abs. 49, 13944 (1955).

viridiflorol and globulol are the four possible diastereoisomers of (II) differing at the asterisked positions. Professor F. Šorm (Prague), to whom we are indebted for a specimen of ledeneglycol, has informed us that he and his co-workers have reached similar conclusions.

We have confirmed the observation of Kyrialov [9] that ledeneglycol on acid treatment followed by dehydrogenation yields 1,6-dimethyl-4-isopropylnapth-5-ol the picrate of which was identical with an authentic specimen prepared from guaiol.[10] The weight of evidence in favour of structure (II) for viridiflorol is so great that the mechanism of this rearrangement must be more complex than Šorm originally proposed.[11]

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[9] N.P. Kyrialov, Sbornik Statei Obshcheĭ Khim. 2, 1617 (1953); Chem. Abs. 49, 5389 (1955).

[10] Pl.A. Plattner and G. Magyar, Helv.Chim. Acta, 24, 191; 1163 (1941).

[11] L. Dolejs, M. Soucek, M. Horak and F. Sorm, Chem. and Ind. 494 (1958); Chem. Listy, 52, 2188 (1958).

Tetrahedron Letters, No. 3, pp. 19-22, 1959. Pergamon Press Ltd.
Printed in Great Britain.

NATURE OF THE SOLVENT EFFECT IN THE INFRARED SPECTRA OF CARBONYL COMPOUNDS

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(Received 10 April 1959)

A number of papers devoted to the investigation of the effect of solvents on the characteristic frequencies of various bonds has appeared in recent literature.[1-5] In some of these papers the authors[1-3] related the observed frequency shifts due to the solvent to some specific property of the solvent such as the dielectric constant or the refractive index on the assumption of the validity of the Kirkwood-Bauer-Magat theory.[6,7] A new approach to the study of the solvent effect can be seen in the recent communications by Archibald and Pullin[4] and by Bellamy, Hallam, and Williams[5] in which the effect of the solvent was shown to depend both on the properties of the solvent and on the character of the bond concerned.

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1 L.N.Fuson and M.L.Josien, J.Phys.Radium 15, 652 (1954).

2 M.L.Josien and L.N.Fuson, J.Chem.Phys. 22, 1169 (1954).

3 N.S.Bayliss, A.R.H.Cole and L.H.Little, Australian J.Chem. 8, 26 (1955).

4 L.B.Archibald and A.D.Pullin, Spectrochim.Acta 12, 34 (1958).

5 L.J.Bellamy, H.E.Hallam and R.L.Williams, Trans.Faraday Soc. 54, 1120 (1958).

6 J.G.Kirkwood, J.Chem.Phys. 2, 351 (1934).

7 E.Bauer and M.Magat, J.Phys.Radium 9, 319 (1938).

In the course of our studies of the infrared spectra of some carbonyl compounds the frequencies of the carbonyl stretching vibration of a number of carboxylic acid derivatives, ketones, and aldehydes were measured in a variety of solvents. It was found that the frequency shifts $\Delta\nu_{CO}$, defined as the differences between the frequencies measured in dilute (0.005-M) solutions in n-hexane and in chloroform, are considerably different for different compounds of the class investigated and depend on the polarity of the carbonyl bond. In particular, a linear relationship was established between the frequency shifts, $\Delta\nu_{CO}$, and the values of the carbonyl stretching frequencies, ν_{CO} (measured in n-hexane), for true carboxylic acid derivatives of the type R-CO-X with X = Halogen,-OR', -NR$\tilde{R}$'. As an example, the plots of $\Delta\nu_{CO}$ vs. ν_{CO} are shown in Fig. 1.for benzoic and acetic acid derivatives for which the following linear relation was found to be obeyed within $\pm$ 2 cm^{-1}:

$$\Delta\nu_{CO} = A\,(1 - \alpha.\nu_{CO}) \qquad (1)$$

with A 283.4 cm^{-1}, α 0.5423.10^{-3} cm for benzoic acid, and A 380.4 cm^{-1}, α 0.5394.10^{-3} cm for acetic acid derivatives. This relation is, however, not valid in the case of ketones and aldehydes.

An analogous behaviour of carboxylic acid derivatives was observed in our previous study of the correlations between the infrared carbonyl stretching frequencies and ultraviolet K-band absorption frequencies.[8] The linear relation between the infrared and ultraviolet frequencies was shown there to be related to a linear relationship between Taft's parameters[9] σ_I and σ_R which can be taken as a measure for the inductive

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[8] O.Exner, M.Horák and J.Plíva, Chem.& Ind. 1174 (1958).

[9] R.W.Taft Jr., J.Amer.Chem.Soc. 79, 1045 (1957).

and mesomeric effects of the substituents X. It was therefore endeavoured to find the relationship between the frequency shifts $\Delta\nu_{CO}$ and the

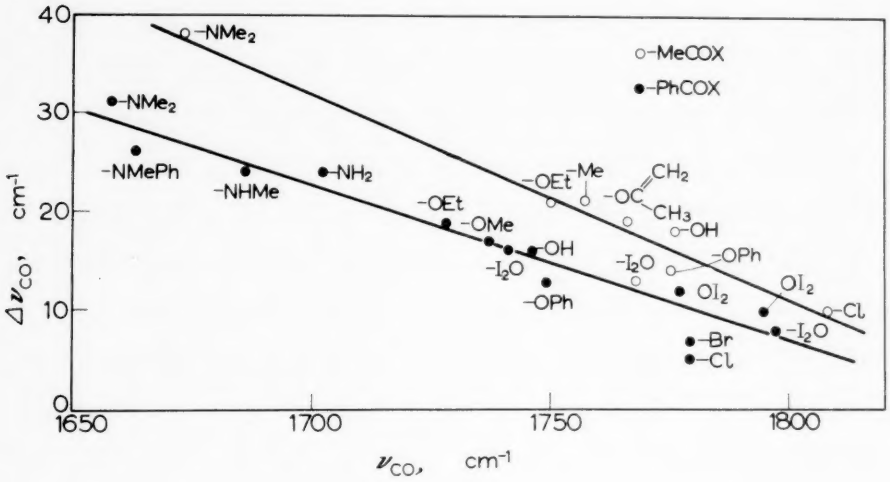

Fig. 1.

Relation between frequency shifts, $\Delta\nu_{CO}$, and carbonyl stretching frequencies, ν_{CO}, for carboxylic acid derivatives, R-CO-X (R = C_6H_5 and R = CH_3).

polar properties of the substituents X as expressed by the σ_I and σ_R constants. Again, a linear relation of the type

$$\Delta\nu_{CO} = \Delta_o(1 + a_I \cdot \sigma_I + a_R \cdot \sigma_R) \qquad (2)$$

was found to be valid not only for the carboxylic acid derivatives for which eq. (I) holds, but in general for aldehydes and ketones as well. The following approximate values of the parameters of eq. (2) were found for the two

cases referred to above: the constants a_I -2.1 and a_R -2.9 are approximately equal for both of these cases and the values of the parameters Δ_o 8 cm^{-1} for R = C_6H_5- and Δ_o 11.5 cm^{-1} for R = CH_3- correspond to the frequency shifts observed for the corresponding aldehydes.

The results of this study show that the solvent effect cannot be simply understood if only the overall properties of the solvent are taken into account, and it is necessary to consider both the properties of the solvent and of the solute and their specific interactions. In the particular case investigated in the present work the differences in frequencies found in a nonpolar solvent (hexane) and in a polar solvent (chloroform) are related to the polar properties of the substituents directly attached to the bond the characteristic frequency of which is studied. Thus it is thought that a thorough investigation of this effect might be of interest from the point of view of the study of the polar properties of organic substituents.

It is proposed to publish a more detailed account of our work in the journal "Collection of Czechoslovak Chemical Communications".

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Papers to be published in future issues of "Tetrahedron"

H.J.E. LOWENTHAL: Selective reactions and modifications of functional groups in steroid chemistry.

T.R. SESHADRI: Recent developments in the chemistry of flavonoids.

Gj. STEFANOVIĆ, Lj. LORENC, R.I. MAMUZIĆ and M. Lj. MIHAILOVIĆ: Anhydrobiisatic acid. 6:12-oxa-5:6:11:12-tetrahydrophenhomazine-6:12-dicarboxylic acid.

C. MECHELYNCK-DAVID and P.J.C. FIERENS: Etudes cinetiques des réactions de solvolyse de chlorures d' α-phenylethyle substitutes. Equations de Hammett, Winstein-Grunwald et Tommila.

R. HUISGEN und H. OTT: Die Konfiguration der Carbonestergruppe und die Sondereigenschaften der Lactone.

F. KORTE, J. FALBE und A. ZSCHOCKE: α-Hydroxyalkaliden-lacton-Umlagerung — IX. Synthese des D,L-Iridomyrmecins und verwandter bicyclischer Lacton.

K.J. CLARK, G.I. FRAY, R.H. JAEGER and Sir ROBERT ROBINSON: Synthesis of D- and L-isoiridomyrmecin and related compounds.

A.H. BECKETT, N.J. HARPER, A.D.J. BOLON and T.H.E. WATTS: Stereochemistry of the reduction of tropinone.

T.L.V. ULBRICHT: Synthesis of pyrinidine-lithium compounds.

N.R. AYYANGAR, B.S. JOSHI and K. VENKATARAMAN: Anthraquinone and anthrone series — XXIII. The non-identity of 1:3:8-trihydroxy-2-hydromethylanthraquinone with versicolorin and a synthesis of damnacanthol and damnacanthal.

F.L. ALLEN, P. KOCH and H. SUSCHITZKY: Heterocyclic fluorine compounds III. Monofluoroxanthones.

W. METLESICS, F.WESSELY und H. BUDZIKIEWICZ: Dienon-Phenol-Umlagerung von Chinolen —II. Beitrag zur Klärung des Reaktionsmechanismes.

E. CLAR: Asymmetric annellation effects —II.

E. CLAR, C.T. IRONSIDE and M. ZANDER: Asymmetric and symmetric annellation effects — III. Benzocoronenes.

A. STREITWIESER, Jr., J.R. WOLFE, Jr., and W.D. SCHAEFFER: Stereochemistry of the primary carbon — X. Stereochemical configurations of some optically active deuterium compounds.

B. EISTERT und F. GEISS: Spektroskopische studien an "trans-fixierten" β-Diketonen und an cyclischen Malonsäure-Estern.

S.A. BARKER, J.S. BRIMACOMBE, A.B. FOSTER, D.H. WHIFFEN and G. ZWEIFEL: Aspects of stereochemistry — II. Intramolecular hydrogen bonding in some monohydroxy derivatives of tetrahydrofuran, tetrahydropyran and 1:3-dioxan.

A.K. BARUA and S. PATTABI RAMAN: Triterpenoids — X. The constitution of albigenic acid - a new triterpenoid sapogenin from Albizzia lebbeck Benth.

P.K. GROVER and T.R. SESHADRI: Constitution of pinastric acid.

G. GAUDIANO, A. QUILICO and A. RICCA: Poly-isoxazoles.

F. SCHEINMANN and H. SUSCHITZKY: Studies in the xanthone series — IV. Preparation and reactions of 2-allyl-1-hydroxyxanthone.

CARL DJERASSI and S. BURNSTEIN: Terpenoids — XXXIX. Iresin (Part 5). Complete structure and absolute configuration.

S.M. KUPCHAN, W.S. JOHNSON and S. RAJAGOPALAN: The configuration of cevine.

M.L. DHAR and T.R. SESHADRI: Ring isomeric change in isoflavones. Synthesis of 5,7-dimethoxy-6-hydroxy-isoflavone, muningin and 5,7-dihydroxy-6-methoxyisoflavone.

KEN'ICHI TAKEDA, TOKUO KUBOTA and (in part) ARIMASA SHIMAOKA: Studies on the steroidal components of domestic plants — XIX. The structure of kogagenin, a sapogenin from Dioscorea tokoro Makino.

J. HARLEY-MASON and A.H. LAIRD: Isolation and structure of the fluorescent substances formed in the oxidative reaction of adrenaline and noradrenaline with ethylenediamine.

J.B. HENDRICKSON: Stereochemical implications in sesquiterpene biogenesis.

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X-RAY ANALYSIS OF THE STRUCTURE OF GELSEMINE HYDROHALIDES

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(Received 27 March 1959)

THE alkaloid gelsemine, in the form of two crystalline hydrohalides, has been subjected to X-ray analysis. The resulting structure satisfies all crystallographic criteria of correctness, and is chemically reasonable.

The structure of gelsemine is of importance in the understanding of biogenetic processes in the parent plant, Gelsemium sempervirens (yellow jasmine). A considerable amount of chemical information has been gathered about the alkaloid, but no acceptable structural model was available to us throughout the present study. The stoichiometric formula, $C_{20}H_{22}N_2O_2$, was known;[1] and evidence existed for the presence of 3,3'-disubstituted oxindole group,[2,3] a tertiary, basic nitrogen atom, bearing one methyl group,[2] in a five-membered ring,[2a] one reactive double bond in a vinyl side chain,[4] and a cyclic ether grouping containing the second oxygen atom.[5] The

* Dept. of Physics, University College, Cardiff.

[1] C. W. Moore, J. Chem. Soc. 97, 2223 (1910); 99, 123 (1911).

[2] L. Marion, Canad. J. Res. 21B, 247 (1943).

[2a] T. Habgood and L. Marion, Canad. J. Chem. 33, 604 (1955).

[3] M. Kates and L. Marion, Canad. J. Res. 29, 27 (1951).

[4] L. Marion and K. Sargeant, J. Amer. Chem. Soc. 78, 5127 (1956).

[5] R. Robinson and M. S. Gibson, Chem. & Ind. 93 (1951).

nature of the remaining ring system was unknown.

Two crystalline salts, the hydrochloride and the hydroiodide, were used in the present investigation. Both salts crystallize in the orthorhombic space group $P2_12_12_1$, with 4 molecules in the cell. The hydrochloride has dimensions $\underline{a}$ = 7.30 A, $\underline{b}$ = 9.00 A, $\underline{c}$ = 26.40 A, with d_{calc} = 1.35 g/cc and d_{obs} = 1.37 g/cc; the hydroiodide has $\underline{a}$ = 7.80 A, $\underline{b}$ = 9.17 A, $\underline{c}$ = 26.90 A, d_{calc} = 1.54 g/cc and d_{obs} = 1.55 g/cc.

Multifilm equi-inclination Weissenberg photographs were used to collect full three-dimensional X-ray data about the $\underline{a}$ and $\underline{b}$ axes of the iodide crystal, and about the $\underline{a}$ axis of the chloride. Cylindrical specimen 0.15 mm in diameter were used, with CuKα radiation, absorption corrections being applied for the hydroiodide (μ = 144 cm^{-1}) but not for the hydrochloride (μ = 21 cm^{-1}).

The hydroiodide was considered first, and the iodine position was found from a three-dimensional Patterson function. The coordinates so obtained were $\underline{x}$ = 0.181, $\underline{y}$ = 0.150, $\underline{z}$ = 0.250. Due to the value of the $\underline{z}$ coordinate, the three-dimensional electron density synthesis, computed with coefficients having iodine phases, contained pseudo mirror planes at $z = \pm 1/4$. Thus is became necessary to disentangle the true structure from its superposed mirror image. A set of peaks could be selected for the atoms of the indole group; and these were introduced into a new structure factor calculation. An electron-density synthesis based on these structure factors confirmed the indole group location, and showed several more atoms. These were in turn included in another cycle. After several cycles of this sort, all atoms were included in a reasonable trial structure.

This structure was subjected to least-squares refinement using the

IBM 704 program of Vand and Pepinsky.[6] The first disagreement factor

$$R = \frac{\Sigma \left| \left| F_{obs} \right| - \left| F_{calc} \right| \right|}{\Sigma \left| F_{obs} \right|}$$

was 0.24; subsequent stages of refinement lowered the R-factor to 0.14 for 1500 symmetry-unrelated reflections, and resulted in a structure which is chemically reasonable.

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The hydrochloride structure was derived by assuming it to be roughly isomorphous with the above structure, and subjecting the coordinates to

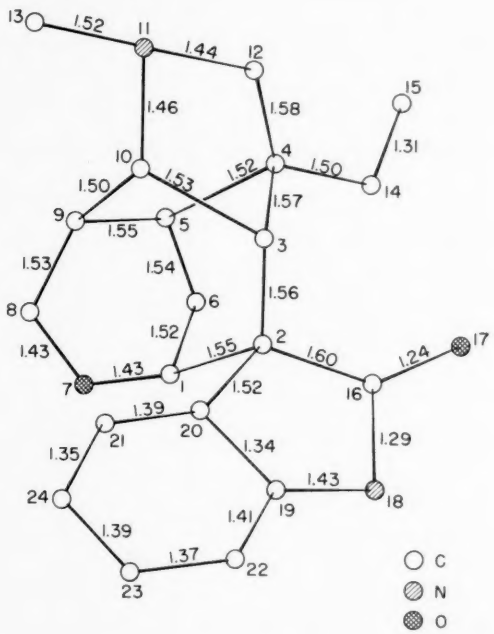

FIG. 1. Bond distances in gelsemine ion, as established from X-ray analysis of gelsemine hydrochloride.

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[6] V. Vand and R. Pepinsky, Z. Krist. 111, 46 (1958).

repeated least-squares refinement cycles. The positions of the halogen and organic components were found to differ significantly in the two derivatives; but least-squares coordinate adjustments in the hydrochloride eventually led to an R value of 0.17 for that structure.

The structure of the organic ion, as derived in the hydrochloride crystal, is shown in Fig. 1. Bond distances, which have standard deviations ranging from 0.01 to 0.03 A, are shown in the figure. A full discussion of the analyses of both crystals, with supporting X-ray data, and a description of the stereochemistry and resonance state of the molecule, will be submitted shortly to this journal. Meanwhile, a table of bond angles, and several figures showing these, are available from the second author (R. P.), as an aid in model construction.

We are delighted to report that the structure given here agrees with one privately reported to us by R.B. Woodward of Harvard University on February 26, 1959, without knowledge of our conclusions. Professor Woodward's arguments made use of biogenetic considerations in conjunction with new chemical evidence, privately communicated to him by Professor Harold Conroy of Yale University, which showed that the vinyl group of gelsemine is attached to a quaternary carbon atom β to N_b. Professor Conroy's similar, independent deduction, as well as other new physical and chemical evidence which is confirmatory of our structure, are reported in his accompanying communication with Dr. J. K. Chakrabarti.[7] We are grateful to Professor Conroy for the opportunity to read his manuscript in advance of publication.

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[7] H. Conroy and J. K. Chakrabarti, Tetrahedron Letters No. 4, 6 (1959).

1959

This X-ray analysis was initiated in the Viriamu Jones Laboratory, University College, Cardiff, by the first and third authors (F. M. L. and A. J. C. W.), and proceeded there successfully from data collection through location of the oxindole group in the hydroiodide. The remainder of the analysis, essentially straightforward from that point, was supported at The Pennsylvania State University by Grant No. A228 from the Institute for Arthritis and Metabolic Diseases, National Institutes of Health. Extensive computations on X-RAC were supported by Contract No. N6onr-26916 with the Office of Naval Research, Physics Branch; and IBM 704 calculations were supported by the Atomic Energy Commission under Contract No. AT(30-1)-1516, and through the generosity of the Curtiss-Wright Corporation at Quehanna, Pa.

We are grateful indeed for the invaluable advice and aid of our colleagues at Penn State: Prof. V. Vand in IBM 704 programming and Prof. Y. Okaya in the structure elucidation.

Tetrahedron Letters, No. 4, pp. 6 - 13, 1959. Pergamon Press Ltd. Printed in Great Britain.

NMR SPECTRA OF GELSEMINE DERIVATIVES. THE STRUCTURE AND BIOGENESIS OF THE ALKALOID GELSEMINE[1]

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(Received 30 March 1959)

THE hexacyclic alkaloid gelsemine, $C_{20}H_{22}O_2N_2$, of Gelsemium sempervirens, contains a vinyl side chain.[2] With the exception of the reaction leading to bromo-allo-gelsemine,[3] which shows that the olefinic center must be located within bonding distance of the carbonyl oxygen associated with the oxindole[4] nucleus, definitive information as to the site of attachment of this vinyl chain has been unavailable.

The 60 mc/sec NMR spectrum[5] of gelsemine shows the twelve strong lines of the ABC (approximately ABX) system,[6] $-CH_X=CH_AH_B$, which comprise three symmetrically split quartets centered at values of τ:[7] (X) 3.72, (A) 4.95 and (B) 5.10, with splittings: (X) 11.3 and 17.8 cps; (A) 1.5 and 11.3 cps and (B) 1.5 and 17.8 cps. Coupling between geminal protons A

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[1] Contribution numbered 1536 from the Department of Chemistry at Yale University.
[2] L. Marion and K. Sargeant, J. Amer. Chem. Soc. 78, 5127 (1956).
[3] R. Goutarel, M.-M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, Helv. Chim. Acta 34, 1139 (1951).
[4] M. Kates and L. Marion, J. Amer. Chem. Soc. 72, 2308 (1950); Canad. J. Chem. 29, 37 (1951).
[5] Spectra were determined in deuterochloroform (99.5%) by Dr. LeRoy Johnson, Applications Laboratory, Varian Associates, Palo Alto, California.
[6] H. J. Bernstein, J. A. Pople and W. G. Schneider, Canad. J. Chem. 35, 65 (1957).
[7] G. V. D. Tiers, J. Phys. Chem. 62, 1151 (1958).

and B within the trigonally hybridized methylene is expected to be small, as it is in styrene,[8] and small coupling is in consonance with the recently calculated variation of J with H-C-H bond angle.[9] The absence of any further splitting in the X set, i.e. the isolation from further spin-spin coupling to a fourth proton Y, requires either that (i) the vinyl group is substituted upon a quaternary carbon or (ii) that a J_{XY} is accidentally zero because of a special conformational relationship of X to Y. In the latter event any minor modification in the steric environment of the vinyl should increase multiplicity in the X spectrum, yet the indoline base, deoxogelsemine,[4] shows the same pattern except that the X multiplet has been shifted to center at $\tau = 3.93$. Acetylation of deoxogelsemine gave N_a-acetyldeoxogelsemine, m.p. 137-139° (Found: C, 75.59; H, 7.38; N, 8.23. $C_{22}H_{26}O_2N_2$ requires: C, 75.40; H, 7.48; N, 7.99.), osmium tetroxide-periodate oxidation of which gave the nor-aldehyde, m.p. 172-174° (Found: C, 71.41; H, 6.73; N, 7.82. $C_{21}H_{24}O_3N_2$ requires: C, 71.57; H, 6.86; N, 7.95.). The NMR spectrum of the aldehyde contains none of the foregoing twelve peaks, but instead a sharp singlet C-CHO resonance line at $\tau = 0.11$ (half-width 1 cps) in confirmation of the postulated quaternary substitution.

Biogenetic considerations suggested the presence of the system $H_2C{=}CH{-}\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}{-}CH_2{-}N_b$; in this environment the N_b-methylene[10] should comprise

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[8] R. W. Fessenden and J. S. Waugh, Abstracts 132nd Meeting of the American Chemical Society, Sept., 1957, p. 72P.

[9] M. Karplus and H. S. Gutowsky, To be published.

[10] T. Habgood and L. Marion, Canad. J. Chem. 33, 604 (1955).

FIG. 1.

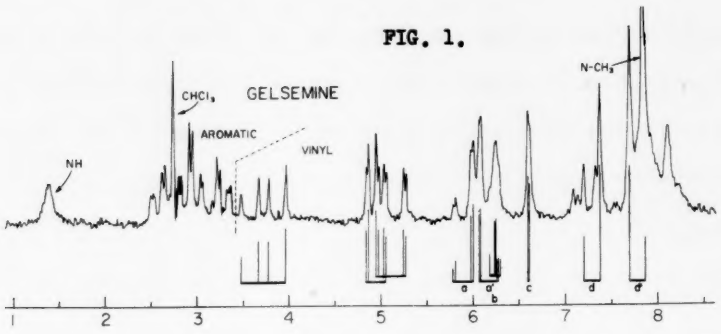


FIG. 2.

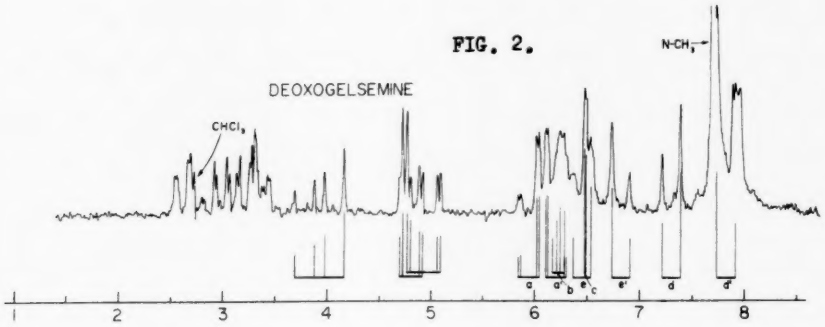
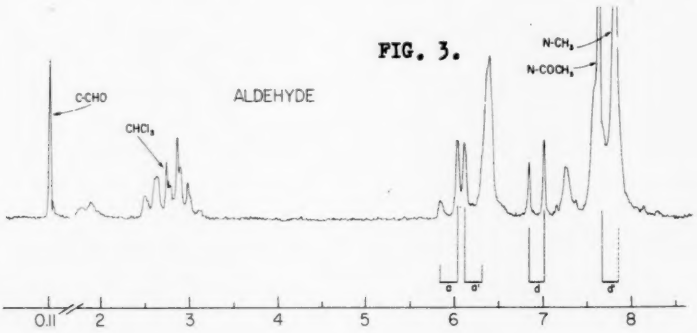


FIG. 3.



an isolated AB system[6] with NMR absorption predicted to be a symmetrical quartet of sharp lines. These appear in the spectra as the doublet pairs d and d', with J = 10.6 cps, with the intensity-spacing relationship in good accord with the theoretical requirement;[6] there is no additional splitting.

[Similarly the N_a-methylene present in deoxogelsemine (but not in gelsemine) appears as the doublet pairs e and e', with J = 10.2 cps, at lower fields because of the conjugation of N_a with the aromatic ring.] The N-methyl[11] appears at τ = 7.84 in the gelsemine curve and at corresponding positions in the other spectra.

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The remaining peaks in the region τ = 6 - 7 represent other C-H protons adjacent to nitrogen or oxygen; the overall integrated intensity is in excellent agreement with four such protons. The sets a and a' form a symmetrical nonequivalence quartet, each member of which is further split into a close doublet, as in the AB segment of an ABX spectrum. The magnitude of the large splitting, 11.5 cps, requires geminal placement of the two protons (upon a saturated carbon); an O-methylene is indicated in view of the low resonance field. The smaller splittings, 0.9 and 1.6 cps, are then caused by coupling with one vicinal proton, as in $>CH-CH_2-O$. The other multiplets, b and c, each with an area given by one proton, do not reveal the large coupling characteristic of the saturated methylene and so must represent separate tertiary protons, as in $O-CH<^{C}_{C}$ and $N-CH<^{C}_{C}$, respectively. Since neither multiplet appears fully resolved, we can deduce only the minimum number of vicinal protons present, as in $O-CH<^{C}_{CH_2}-$ (or $O-CH<^{CH<}_{CH<}$) and $N-CH<^{C}_{CH<}$.

We turn now to a more detailed biogenetic argument. The proposed precursor (III) which bears the same essential relation (N_b-dehydrogenation-N_b-methylation) to corynoxeine (I)[12] or rhyncophylline (II)[13] as does

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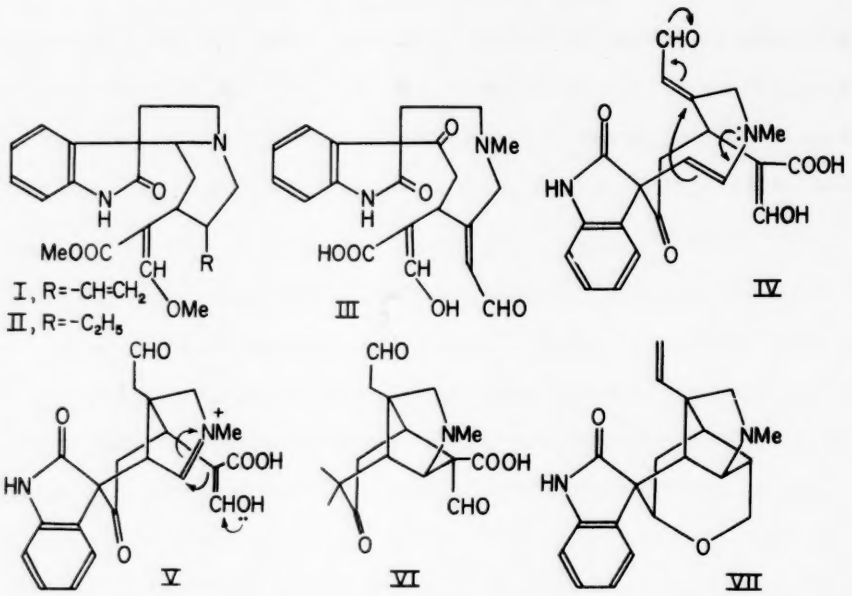
[11] B. Witkop, J. Amer. Chem. Soc. 70, 1424 (1948).

[12] N. An Cu, R. Goutarel and M.-M. Janot, Bull. Soc. Chim. Fr. 1292 (1957).

[13] J. C. Seaton and L. Marion, Canad. J. Chem. 35, 1102 (1957).



vomicine to strychnine, may be derived from equivalents of tryptamine and 3,4-dioxyphenylalanine according to accepted principles.[14] Further dehydrogenation at N_b gives IV; Michael addition of the enamine to the conjugated system establishes the quaternary carbon and forms the five-membered ring[10] enclosing N_b. The intermediate (V) is disposed to internal Mannich condensation, to give VI, whence decarboxylation, completion of the oxide ring and adjustment of oxidation state results in VII, as a

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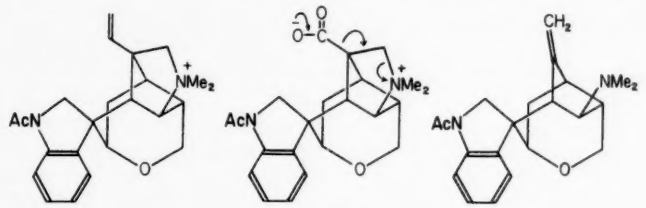
[14] Cf. R. Robinson, Structural Relations of Natural Products. Oxford University Press (1955); J. E. Saxton, Quart. Rev. 10, 120 (1956); for an early application to the biogenesis of strychnine, Cf. R. B. Woodward, Nature, Lond. 162, 155 (1948); for a discussion of the related biogenesis of corynantheine, Cf. M.-M. Janot and R. Goutarel, Bull. Soc. Chim. Fr. [5] 18, 588 (1951).

structure for gelsemine.[15] We note that the bond formed in the Mannich reaction (V ⟶ VI) is identical in principle to linkages characteristic of sarpagine, ajmaline and others, but that the bond formed in the Michael change (IV ⟶ V) is, as yet, unique.

The following new degradative sequence provides rigorous proof of the presence in gelsemine of the chain $H_2C{=}CH{-}\overset{C}{\underset{C}{C}}{-}CH_2{-}N_b$, and is otherwise fully consistent with the structure VII. N_a-acetyldeoxogelsemine gave N_a-acetyldeoxogelsemine N_b-methiodide, m.p. 297-299°, dec. (Found: C, 56.30; H, 6.05; N, 5.65. $C_{23}H_{29}O_2N_2I$ requires: C, 56.10; H, 5.94; N, 5.69.). Oxidation of the corresponding N_b-methohydroxide (VIII) (alkaline permanganate) provided the betaine (IX) with υ_{max} = 1597 cm^{-1}. Concerted decarboxylation-β-elimination in dilute (0.1%) solution[16] in boiling dimethylformamide gave the basic



VIII IX X

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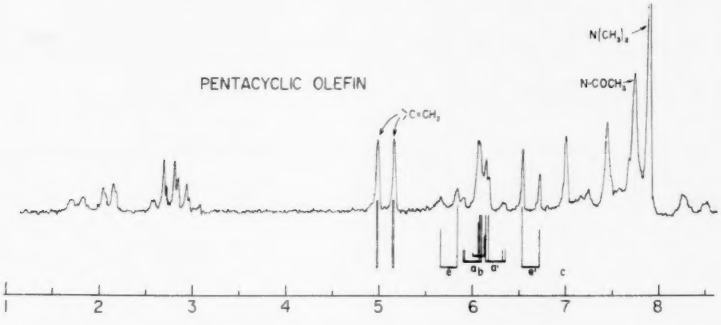
[15] The structure (VII) is consistent with all other previous results, of which the more significant include (i) the participation of the oxindole oxygen in bromination at the vinyl,[3] accountable in terms of the proximity of these groups, and (ii) the failure of Hofmann elimination with gelsemine methohydroxide [R. Goutarel, M.-M. Janet, V. Prelog and R. P. A. Sneeden, Helv. Chim. Acta 34, 1962 (1951); T. Habgood, L. Marion and H. Schwarz, Ibid. 35, 658 (1952); V. Prelog, J. B. Patrick and B. Witkop, Ibid. 35, 640 (1952)], a result of the steric impossibility of any olefinic product. Witkop[11] has reported the isolation of a base $C_{11}H_{11}N$, from the zinc dust degradation of gelsemine, which he regarded as a dimethyl- or ethyl- quinoline or isoquinoline. The 4,7-dimethylisoquinoline skeleton is present intact in VII.

[16] Bimolecular reaction, leading to the methyl ester of the corresponding tertiary base, occurred to the exclusion of the desired intramolecular elimination when the betaine (IX) was merely heated

pentacyclic olefin (X), m.p. 130° (Found: C, 74.25; H, 7.47; N, 8.26. $C_{21}H_{26}O_2N_2$ requires: C, 74.52; H, 7.74; N, 8.28.), further characterized by its methiodide (XI), m.p. 273-275° (from aqueous methanol) (Found: C, 54.09; H, 6.15; O, 7.44; N, 5.76; I, 26.40. $C_{22}H_{29}O_2N_2I.\frac{1}{2}H_2O$ requires: C, 54.10; H, 5.99; O, 8.19; N, 5.74; I, 25.99.). The 60 mc/sec NMR spectrum[5] of X shows a symmetrical pair of peaks in the $C{=}CH_2$ region, at τ = 4.98 and 5.15 (area of each = 1 proton) and agrees with the other features



implied.[17] Microhydrogenation (platinum-acetic acid) of X gave the dihydro derivative, m.p. 165-167°, which contains an additional C-methyl (Found: C-Me, 7.09. $C_{21}H_{28}O_2N_2$ requires: one C-Me, 4.42; two C-Me, 8.83.), after absorption of 1.0 mole of hydrogen. Oxidation[18] (osmium tetroxide-periodate)

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in vacuo in the absence of any diluent. In sufficiently dilute solution, as would be expected, the unimolecular reaction predominates over the bimolecular transmethylation.

17 The spectrum in the exo-methylene region is that expected of the AB system[6] when $J_{AB} \cong 0$; the weak coupling within the trigonal methylene has been mentioned (vide supra). The spectrum of X does not contain the N_b-methylene nonequivalence quartet of the precursors. The other multiplets (a,a', b, c, e and e') are assigned as in the previous spectra.

18 The oxidations yielded as well a neutral fraction with ν_{max} ~1720 cm^{-1}, believed to arise via (reverse Mannich) decomposition of the five-membered keto-base.

of X gave a keto-base with ν_{max} = 1748 cm^{-1}, evidence for substitution of the exo-methylene at the five-membered ring.

We were delighted to learn recently that the structure (VII) for gelsemine, which we had deduced on the basis of these arguments, and which is fully consonant with, though not proved in all details by, the evidence given in this communication, is identical with that entirely independently deduced by Lovell, Pepinsky and Wilson from elegant X-ray crystallographic studies, which are described in an accompanying communication. We are grateful to Professor Pepinsky for the opportunity to read his manuscript in advance of publication.

Acknowledgments —— This research is supported by grants from the National Science Foundation (NSF-G6586) and from the Eli Lilly Research Laboratories. Microanalyses were performed by W. Manser, E. T. H., Zurich and by Dr. S. M. Nagy, M. I. T.

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seco-isoLARICIRESINOL, A NEW LIGNAN FROM *Podocarpus spicatus*

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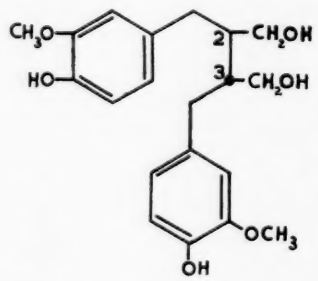
(Received 14 April 1959)

IN a continued investigation of the heartwood constituents of *Podocarpus spicatus* we have isolated a further lignan, m.p. 113.5°, $[\alpha]_D^{25}$ - 35.6°, in addition to the previously reported matairesinol[1] and conidendrin.[1] The compound has formula $C_{20}H_{26}O_6$, possesses two methoxy groups and four hydroxy groups, two of which are phenolic, and is formulated as a lignan by the close similarity of the ultra-violet spectrum with those of matairesinol, conidendrin and isolariciresinol. With the assumption that the substitution pattern is of the common 4-hydroxy-3-methoxy type the structure of the lignan can only be formulated as (-)-2:3-bis(4'-hydroxy-3'-methoxybenzyl)-butan-1:4-diol (I).



[1] H. Erdtman in *Modern Methods of Plant Analysis* Vol. III, pp. 428-449. Springer-Verlag, Germany (1955).

The lignan has not been previously isolated from natural sources but has been detected by paper chromatography among the hydrogenation products of pinoresinol.[2] To indicate its structural relationship the name seco-isolariciresinol is proposed for the lignan.

The structure has been confirmed by a synthesis from (-)-matairesinol. $LiAlH_4$ reduction of the dibenzyl derivative of matairesinol gave a diol, hydrogenolysis of which removed the benzyl groups to give a product which was identical in all respects with seco-isolariciresinol. From the work of Schrecker and Hartwell[3] the synthesis leads to the absolute configuration of seco-isolariciresinol as 2L, 3D.

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[2] K. Freudenberg and L. Knof, Chem. Ber. 90, 2857 (1957).

[3] A. W. Schrecker and J. L. Hartwell, J. Amer. Chem. Soc. 77, 432 (1955); 79, 3827 (1957); J. Org. Chem. 21, 381 (1956).

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MECHANISM OF THE DIELS-ALDER REACTION

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(Received 16 April 1959)

WOODWARD and Katz[1] have recently proposed a new mechanism for the Diels-Alder reaction, based on a remarkable rearrangement undergone by a hydroxy derivative of the dimer of cyclopentadiene. This mechanism requires the reaction to occur in two stages, the two bonds linking diene to dienophil being formed separately.

If such a mechanism operates, one would expect little difference in reactivity between a monosubstituted ethylene CH_2=CHX and a corresponding disubstituted ethylene XCH=CHX; for only one of the substituents X can be well placed to stabilise the transition state. The situation would be similar to that in radical addition reactions to ethylene derivatives where compounds of the type CHX=CHX do not react more readily than analogous vinyl derivatives CH_2=CHX.

If on the other hand the reaction takes place by a one-step mechanism, as many authors have suggested,[2] both substituents in CHX=CHX can stabilise

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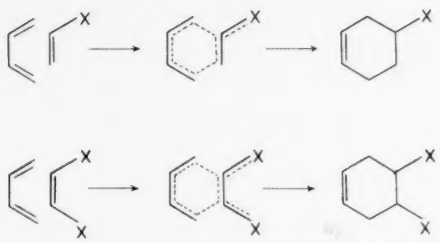
[1] R.B. Woodward and Thomas J. Katz, Tetrahedron 5, 70 (1959).

[2] cf. Evans, Trans. Faraday Soc. 35, 824 (1939).

the corresponding symmetrical transition state, equally well, i.e.



Here one would expect XCH = CHX to be much more reactive than CH_2=CHX, the difference in reactivity between them being similar to the difference in reactivity between CH_2=CHX and ethylene itself.

Some years ago I examined the Diels-Alder reactions of isoprene with acrolein and with maleic anhydride. The second order rate constants for reactions in anisole at 100°C were:

acrolein, 1.82×10^{-4} ; maleic anhydride, 1.29×10^{-2} $ml^{-1}s^{-1}$.

Since the conjugative effect of formyl is greater than that of anhydride carbonyl, the difference in reactivity between maleic and acrylic anhydrides would presumably be still greater. Moreover extrapolation of the data reported by Rowley and Steiner[3] for the reaction between butadiene and ethylene gives a calculated second order rate constant at 100°C of 3×10^{-6} $ml^{-1}s^{-1}$. Since isoprene is if anything more reactive than butadiene, it seems clear that the differences in rate constants between ethylene and acrolein, and between acrolein and maleic anhydride, are very similar (~ 70).

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[3] Rowley and Steiner, Disc. Faraday Soc. 10, 198 (1951).

These observations provide very strong evidence for the one-step mechanism for the Diels-Alder reaction, proceeding through a cyclic pseudo-aromatic[2] transition state.

Full details of this work, in which the rates of the isoprene-maleic anhydride and isoprene-acrolein reaction were measured over a range of temperature in a variety of solvents, will be published shortly. The effect of solvent on the rates of reaction also seemed to favour the one-step mechanism.

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It may be added that the evidence given by Woodward and Katz is not directly relevant to the mechanism of the Diels-Alder reaction. In the transition state for their isomerisation, the diene and dienophil are linked by a full bond. In the transition state for their Diels-Alder mechanism, the components are linked by a partial bond. The two transition states are quite dissimilar. It might be added that if they were <u>not</u> dissimilar, then the rearrangement observed by Woodward and Katz could not occur; for the transition state could equally well dissociate into two molecules of diene.

Since the transition state for the rearrangement observed by Woodward and Katz is necessarily different to the transition state for the Diels-Alder reaction, the two reactions are unrelated and no conclusions concerning the mechanism of one can be drawn from that of the other.

ABSTRACTS OF SOME ACCEPTED "TETRAHEDRON" PAPERS

1959

SPEKTROSKOPISCHE STUDIEN AN „TRANS-FIXIERTEN" β-DIKETONEN UND AN CYCLISCHEN MALONSÄURE-ESTERN

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Zusammenfassung—Es wird der IR- und UV-spektroskopische Nachweis der Abhängigkeit des Keto–Enol–Gleichgewichts vom Lösungsmittel und des Enol–Enolat–Gleichgewichts vom pH für „trans-fixierte" β-Diketone vom Typus des *Dimedons* bestätigt. Cyclische Malonsäureester vom Typus der *Meldrum*-Säure (*Iso*propylidenmalonat) sind in festem Zustand und in OH-gruppenfreien Solventien nicht enolisiert; in Methanol wurde nur die UV-Bande des Enolat-Anions gefunden, die bei Verringerung des pH-Wertes reversibel verschwindet, ohne dass eine der undissoziierten Enolform zuzuordnende Bande auftritt. Einer Hypothese, dass das Keto–Enol–Gleichgewicht „trans-fixierter" β-Dicarbonylverbindungen lösungsmittel-unabhängig sei, wird auf Grund experimenteller Gegenbeweise widersprochen.

Abstract—IR and UV spectra have confirmed that in "trans-fixed" β-diketones of the dimedone (methone) type, keto–enol–equilibrium depends on the solvent, and the enol–enolate–equilibrium on the pH. Cyclic malonic esters of the type of Meldrum's acid (*iso*propylidene malonic acid) are not enolized either in the solid state or in solvents free of OH-groups; in methanol only the UV band of the enolate anion was found, which on diminishing the pH disappeared reversibly without the appearance of band associated with the undissociated enol form. An hypothesis that keto–enol–equilibrium of "trans-fixed" β-dicarbonyl compounds is independent of the solvent has been disproved experimentally.

TRITERPENOIDS—X

THE CONSTITUTION OF ALBIGENIC ACID—A NEW TRITERPENOID SAPOGENIN FROM *ALBIZZIA LEBBECK* BENTH.

A. K. BARUA and S. PATTABI RAMAN
Department of Chemistry, Bose Institute, Calcutta

Abstract—The constitution of albigenic acid—a new triterpenoid sapogenin from the beans of *Albizzia lebbeck* Benth, has been established as 3β:16α-dihydroxyolean-13(18)-en-28-oic acid and its partial synthesis from echinocystic acid is described.

A list of papers to be published in future issues of "Tetrahedron"

H. J. E. LOWENTHAL : Selective reactions and modification of functional groups in steroid chemistry.

Gj. STEFANOVIĆ, Lj. LORENC, R. I. MAMUZIĆ and M. Lj. MIHAILOVIĆ : Anhydrobiisatic acid. 6:12-oxa-5:6:11:12-tetrahydrophenhomazine-6:12-dicarboxylic acid.

T. R. SESHADRI : Recent developments in the chemistry of flavonoids.

C. MECHELYNCK - DAVID and P. J. C. FIERENS : Études cinetiques des réactions de solvolyse de chlorures d'α-phenylethyle substitutes. Equations de Hammett, Winstein-Grunwald et Tommila.

R. HUISGEN und H. OTT : Die Konfiguration der Carbonestergruppe und die Sondereigenschaften der Lactone.

F. KORTE, J. FALBE und A. ZSCHOCKE : α-Hydroxyalkyliden-lacton-Umlagérung -IX. Synthese des D,L-Iridomyrmecins und verwandter bicyclischer Lactone.

K. J. CLARK, G. I. FRAY, R. H. JAEGER and Sir ROBERT ROBINSON : Synthesis of D- and L-isoiridomyrmecin and related compounds.

A. H. BECKETT, N. J. HARPER, A. D. J. BOLON and T. H. E. WATTS : Stereochemistry of the reduction of tropinone.

T. L. V. ULBRICHT : Synthesis of pyrimidine-lithium compounds.

N. R. AYYANGAR, B. S. JOSHI and K. VENKATARAMAN : Anthraquinone and anthrone series - XXIII. The non-identity of 1:3:8-trihydroxy-2-hydroxymethylanthraquinone with versicolorin and a synthesis of demnacanthol and damnacanthal.

F. L. ALLEN, P. KOCH and H. SUSCHITZKY : Heterocyclic fluorine compounds-III. Monofluoro-xanthones.

W. METLESICS, F. WESSELY und H. BUDZIKIEWICZ : Dienon- Phenol- Umlagerung von Chinolen - II. Beitrag zur Klärung des Reaktionsmechanismus.

E. CLAR : Asymmetric annellation effects - II.

E. CLAR, C. T. IRONSIDE and M. ZANDER : Asymmetric and symmetric annellation effects - III. Benzocoronenes.

A. STREITWIESER, Jr., J. R. WOLFE, Jr. and W. D. SCHAEFFER : Stereochemistry of the primary carbon - X. Stereochemical configurations of some optically active deuterium compounds.

B. EISTERT und F. GEISS : Spektroskopische studien an "trans-fixierten" β-Diketonen und an cyclischen Malonsäure-Estern.

S. A. BARKER, J. S. BRIMACOMBE, A. B. FOSTER, D. H. WHIFFEN and G. ZWEIFEL : Aspects of stereochemistry - II. Intramolecular hydrogen bonding in some monohydroxy derivatives of tetrahydrofuran, tetrahydropyran and 1:3-dioxan.

A. K. BARUA and S. PATTABI RAMAN : Triterpenoids - X. The constitution of albigenic acid - a new triterpenoid sapogenin from Albizzia lebbeck Benth.

P. K. GROVER and T. R. SESHADRI : Constitution of pinastric acid.

G. GAUDIANO, A. QUILICO and A. RICCA : Poly-isoxazoles.

F. SCHEINMAN and H. SUSCHITZKY : Studies in the xanthone series - IV. Preparation and reactions of 2-allyl-1-hydroxyxanthone.

S. M. KUPCHAN, W. S. JOHNSON and S. RAJAGOPALAN : The configuration of cevine.

M. L. DHAR and T. R. SESHADRI : Ring isomeric change in isoflavones. Synthesis of 5,7-dimethoxy-6-hydroxyisoflavone, muningin and 5,7-dihydroxy-6-methoxyisoflavone.

J. HARLEY-MASON and A. H. LAIRD : Isolation and structure of the fluorescent substances formed in the oxidative reaction of adrenaline and noradrenaline with ethylenediamine.

KEN'ICHI TAKEDA, TOKUO KUBOTA and (in part) ARIMASA SHIMAOKA : Studies on the steroidal compounds of domestic plants - XIX. The structure of kogagenin. A sapogenin from Dioscorea tokoro, Makino.

J. B. HENDRICKSON : Stereochemical implications in sesquiterpene biogenesis.

RYUJI TACHIKAWA : Synthesis of some isoquinoline derivatives.

R. GAY et A. HOREAU : Structure moleculaire et activite oestrogene - XVII. Comparaison des configurations absolues des acides bisdehydrodoisynolique normal et α,α-dimethyl β-ethyl allenolique physiologiquement actif.

L. van HOVE : Contribution à l'étude des alcaloides de l'holarrhéna congolensis Stapf. Structure de l'holarrhénine.

1959

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MECHANISM OF THE CHROMIC ACID OXIDATION OF ALDEHYDES

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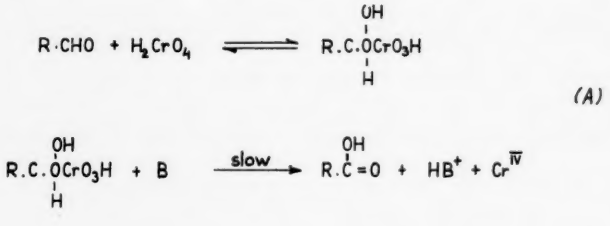
(Received 20 April 1959)

GRAHAM and Westheimer,[1] and Wiberg and Mill[2] have recently put forward mechanism (A) for the chromic acid oxidation of aldehydes. This mechanism is analogous to the "ester" mechanism earlier[3] proposed for the oxidation of alcohols.



(A)

Some time ago we expressed the view[4] that the facts concerning the alcohol oxidation can be better explained by a cyclic mechanism consisting in a rate determining hydride ion transfer from the substrate to the oxidising agent.

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[1] G. T. E. Graham and F. H. Westheimer, J. Amer. Chem. Soc. 80, 3030 (1958).

[2] K. B. Wiberg and T. Mill, J. Amer. Chem. Soc. 80, 3022 (1958).

[3] M. Cohen and F. H. Westheimer, J. Amer. Chem. Soc. 74, 4387 (1952); and earlier papers.

[4] J. Rocek and J. Krupicka, Coll. Czech. Chem. Comm. 23, 2068 (1958); Chem. & Ind. 1668 (1957); Preliminary communication.

The similarity between the aldehyde and the alcohol oxidations is generally accepted; and we now wish to propose an analogous cyclic mechanism for oxidation of aldehydes, in their hydrated form (B).

(B)

The most striking difference between the two mechanisms, (A) and (B), is the type of hydrogen transfer: the former requires a proton transfer to a base, the latter assumes a hydride anion transfer. Hence, electronegative groups would be expected to accelerate the oxidation if mechanism (A) is correct, and retard it if mechanism (B) holds.

The enhancement of rate with increasing electronegativity of meta or para substituents in the aromatic nucleus of benzaldehyde has, in fact, been adduced as one of the most important arguments in support of mechanism (A).

In this paper we wish to report the results of rate measurements of the chromic acid oxidation of a series of acetaldehydes with an increasing number of electronegative substituents. These aldehydes, unlike the substituted benzaldehydes used by Wiberg and Mill,[2] are either known to be fully hydrated, or their degree of hydration is known.[5] This enables us to determine the true oxidation rate of the aldehyde hydrate. The results of our measurements are given in Fig. 1, where the logarithms of the rate constants are plotted against Taft's σ^* constants[6] as a measure of substituent polarity.

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[5] R. P. Bell and J. C. Clunie, Trans. Faraday Soc. 48, 393 (1952).

[6] R. W. Taft, Steric Effects in Organic Chemistry (Edited by M. S. Newman) p. 556. Wiley, New York (1956).

1959

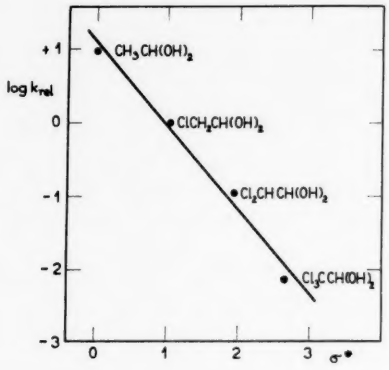

FIG. 1. Dependence of relative rate of aldehyde hydrate oxidation on the σ^* value of the (halogen) alkyl group.

From this graph it is evident that with increasing electronegativity of the substituent, R, the reaction rate rapidly decreases, the value of ϱ^* being approximately - 1.2. This result, indicating that the oxidation is facilitated by high electron density at the C-H bond, is in full agreement with our mechanism (B) involving hydride anion abstraction.

The results of Wiberg and Mill[2] in the aromatic series find a ready alternative explanation. The concentrations of the hydrate in solutions of aromatic aldehydes are known to be small, the equilibrium being strongly in favour of the free aldehydes. The actual concentration of the geminal diol in the particular cases has not been determined but it is likely to be increased by electronegative substituents; the effect of this increase in concentration may well outweigh the decrease in reactivity.

A more detailed discussion and additional experimental material will be published in the Coll. Czech. Chem. Comm. in due course.

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THE STRUCTURE OF CYPRIDINA LUCIFERIN

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(Received 22 April 1959)

CYPRIDINA luciferin was obtained crystalline, and preliminary results on the constitution of luciferin using the crystalline material have already been reported.[1]

Molecular Weight and Molecular Formula of Cypridina Luciferin

The molecular weight of crystalline luciferin was estimated to be 470 by various methods; Barger (357), oxidative titration with ferricyanide (467), the U. V. absorption of hydroluciferin (478), hydrogenation of luciferin (498), and analyses of chlorine and nitrogen.

The percentage analysis is as follows:

	C	H	N	O	Cl	Ash	M. W.
Found	53.2	6.38	18.86	6.7	16.2	0	
Calcd. for $C_{21}H_{28}O_2N_6 \cdot 2HCl$	53.7	6.39	17.91	6.8	15.1	0	469

The results from hydrolysis experiments and pKa' measurements of luciferin dihydrochloride were also taken into consideration in deducing the molecular formula of $C_{21}H_{28}O_2N_6 \cdot 2HCl$.

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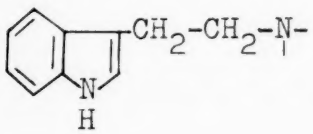
[1] O. Shimomura, T. Goto and Y. Hirata, Bull. Chem. Soc. Japan 30, 929 (1957).

1959

Deduction of the Structure of Hydroluciferin

When hydrogenated with Adams' platinum oxide catalyst, luciferin absorbed 3 moles of hydrogen and was converted into a compound which showed an U. V. absorption spectrum suggesting the presence of a β-indolethylamino group. A positive Ehrlich reaction showed that the α-position of the indole nucleus is free and hydrolysis of hydroluciferin afforded tryptamine.

Hydroluciferin thus contains the grouping



The Sakaguchi reaction is positive for hydroluciferin as well as for luciferin and oxyluciferins, and this shows the presence of a monosubstituted guanidino group which in turn is confirmed by the isolation of γ-guanidinobutyric acid by acid hydrolysis in the presence of oxygen(air). γ-Guanidinobutyric acid was produced only when the hydrolysis was conducted under the presence of oxygen. Thus the γ-guanidinobutyric acid moiety is not contained in a peptide linkage; it is present in a more reduced state.

Isoleucine was also obtained by hydrolysis. Accordingly hydroluciferin is composed of tryptamine, γ-guanidinobutyric acid and isoleucine. This accounts for 21 carbon atoms and 6 nitrogen atoms.

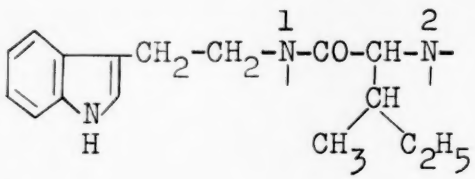
Partial hydrolysis with $Ba(OH)_2$ gave a fraction with positive ninhydrin and Ehrlich reactions. Extraction of this fraction and further hydrolysis

under the same conditions gave isoleucine and tryptamine, and thus these two components are linked by a peptide bond.

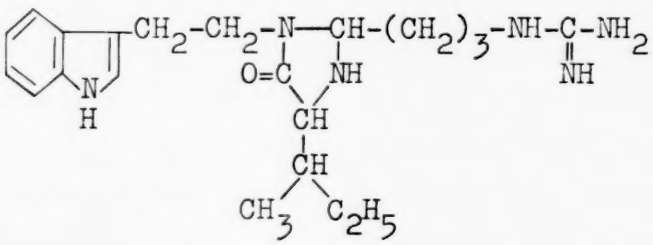
In spite of the positive (but weak) ninhydrin reaction, hydroluciferin contains no primary amino group from the following facts:

(a) After treatment with 2,4-D. N. F. B., hydroluciferin did not afford D. N. P. isoleucine by hydrolysis.

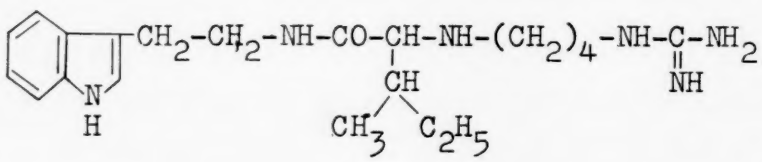
(b) Hydroluciferin did not react with nitrous acid.



Attachment of the γ-guanidino butyric acid group to positions 1 and 2 to afford the cyclic structure is favored by the following facts.



The alternative possibility of attachment to position 2 only would give a chain structure.



which would be rather stable contrary to the extreme instability of hydroluciferin.

Hydroluciferin has pKa's at ca. 5.2 and 12.0 (guanidino group) in 33 % MeOH. The lower pKa' at 5.2 is only explicable by assigning to it the cyclic secondary amino group with a β-NCO group. The pKa's of secondary amines are generally around 9.5. The Dragendorf reaction is positive.

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Deduction of the Structure of Luciferin

It appears that the skeletal structure of hydroluciferin is identical with that of luciferin.

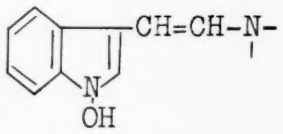
The Adamkiewitz and Ehrlich (Neubauer-Rhode) reaction were negative. This shows that the indole nucleus on luciferin is substituted either at the nitrogen or at the α-position. This substituent should be easily detached by catalytic hydrogenation, since a β-indolethylamine derivative was produced upon hydrogenation of luciferin. This property taken in conjunction with the pKa' at 8.3 in 33 % MeOH is most suitably accounted for by the presence of a N-hydroxy indole group in luciferin. The titration curve shows that the pKa' at 8.3 must be attributed to the acidic group. A few N-hydroxy indole model compounds showed that the pKa' of these are of the order of ca. 8.3, and that the >N-OH group is converted into >NH by catalytic hydrogenation with platinum oxide catalyst. This is further supported by the following facts:

(a) Aromatic primary amine derivatives could not be produced by mild hydrolysis of luciferin with $Ba(OH)_2$; this excludes the possibility of the presence of α-OH group.

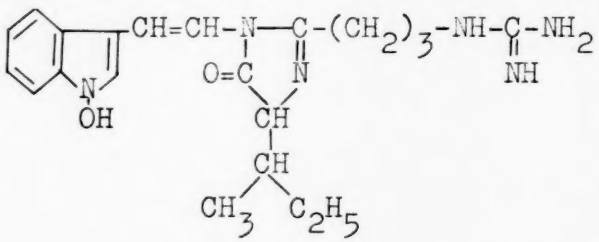
(b) Ferricyanide oxidation of N-hydroxy indole compounds gave

oxidation results similar to those obtained with luciferin.

The λ_{max} of luciferin at 435 mμ suggests that the chromophore of the indole moiety is further extended as follows and this also accounts for the production of glycine by hydrolysis and also for the absorption of hydrogen.



Oxidation of luciferin with hydrogen peroxide in the presence of ammonia gave crystalline oxyluciferin C, the hydrolysis of which under various conditions produced no isoleucine. However, the production of isoleucine is resumed if oxyluciferin C is reduced prior to hydrolysis. These facts suggest the presence of an N(isoleucine)-oxide group in oxyluciferin C. The facts that secondary amino groups are not converted into N-oxide under the condition employed and that an additional double bond is present in luciferin (from the molecular formula and hydrogenation of luciferin) lead to the presence of the group N(isoleucine)=C< and thus so the present tentative structure of



The exact position of the double bond in the 4(or 5)-imidazolone ring is not established. It is provisionally placed as shown from the results of hydrolysis which did not afford any acid like $HOOC-\underset{OH}{CH}-\underset{CH_3}{CH}-C_2H_5$, and also in order to account for its rather long wavelength absorption maximum.

The guanidine and oxo-diaza groups are responsible for the formation of a dihydrochloride, whereas the N-OH group in the indole moiety gives rise to the pKa' at 8.3.

1959

Tetrahedron Letters, No. 5, pp. 10-13, 1959. Pergamon Press Ltd. Printed in Great Britain.

RESOLUTION DURING TOTAL SYNTHESIS OF RESERPINE

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(Received 23 April 1959)

IN their brilliant total synthesis, Woodward et al.[1] carried out the resolution in the final stage by means of (+)-camphor-10-sulfonic acid and obtained (-)-reserpine, identical with the natural product. With respect to technical preparation, placing the resolution at the end of a long synthesis is unfavourable. Therefore, the work of Velluz et al.,[2] who performed the resolution in the stage of cis-5-hydroxy-8-oxo-1,4,5,8,9,10-hexahydro-1-naphthoic acid - using the first Woodward's variant [3] of the synthesis in the opening phases, is a considerable improvement. This method, however, is impracticable in the very advantageous second Woodward's variant.[4]

In order to achieve the resolution at the stage of the hydroxy lactone Ia,[1,5] we prepared its acid phthalate Ib (m.p. 215°; found : C, 67,08;

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1 R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, Tetrahedron 2, 1 (1958).

2 L. Velluz, G. Muller, R. Joly, G. Nominé, J. Mathieu, A. Allais, J. Warnant, J. Valls, J. Bucourt and J. Jolly, Bull. Soc. Chim. Fr. 673 (1958).

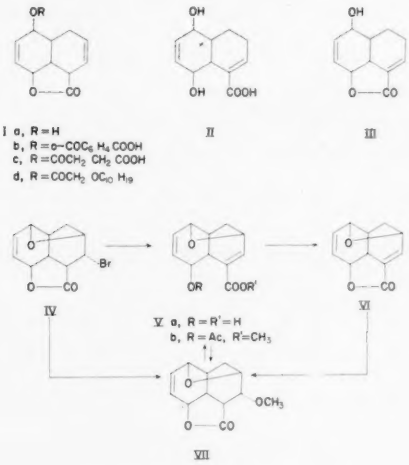
3 R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, J. Amer. Chem. Soc. 78, 2023 (1956).

4 R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, J. Amer. Chem. Soc. 78, 2657 (1956).

5 E. Adlerová, L. Bláha, M. Borovička, I. Ernest, J. O. Jílek, B. Kakáč, L. Novák, M. Rajšner and M. Protiva, Coll. Czech. Chem. Comm. 24, In press (1959).

H, 4,88; COOH, 13,62. $C_{19}H_{16}O_6$ requires C, 67,05; H, 4,75; COOH, 13,22) and acid succinate Ic (m.p. 142°; found: C, 61,91; H, 5,81; COOH, 15,40. $C_{15}H_{16}O_6$ requires C, 61,64; H, 5,52; COOH, 15,39) and by way of the brucine salt of the former (m.p. 218-222°; $[\alpha]_D^{20}$ + 5° in $CHCl_3$; found: C, 68,92; H, 6,01; N, 3.93. $C_{42}H_{42}N_2O_{10}$ requires C, 68,65; H, 5.76; N, 3,81) we obtained the (+)-acid phthalate Ib (m.p. 190-193°; $[\alpha]_D^{20}$ + 57° in $CHCl_3$; found: C, 67,15; H, 4,92; COOH, 13,16. $C_{19}H_{19}O_6$ requires C, 67,05; H, 4,75; COOH, 13,22). Also by crystallisation of the (-)-menthoxyacetate Ib it was possible to achieve the resolution and to obtain one diastereoisomer in pure form (m.p. 128-129°; $[\alpha]_D^{20}$ -36° in $CHCl_3$; found C, 71,39; H, 8,44. $C_{23}H_{32}O_5$ requires C, 71,10; H, 8.30). Attempts to transform these substances (Ib, Id) back to the hydroxy lactone Ia by hydrolysis led, however, to complicated and non-crystallising mixtures.

By alkaline hydrolysis of the hydroxy lactone Ia we aquired the new dihydroxy acid $C_{11}H_{14}O_4$, m.p. 175°, also resolvable in the form of its



brucine salt (m.p. 143-147°; $[\alpha]_D^{20}$ -71° in 90 % CH_3OH; found: C, 64,56; H, 7,12; N, 4,31. $C_{34}H_{40}N_2O_8.1\frac{1}{2}H_2O$ requires C, 64,65; H, 6,86; N, 4,44) and obtainable in the (-)-form (m.p. 185°; $[\alpha]_D^{20}$ -162° in 90 % CH_3OH; found: C, 63,19; H, 6,85. $C_{11}H_{14}O_4$ requires C, 62,84; H, 6,71). This dihydroxy acid gave by the action of N,N -dicyclohexylcarbodiimide the hydroxy lactone $C_{11}H_{12}O_3$ (found: C, 68,73; H, 6,43; requires C, 68,73; H, 6,29), melting at 123°, i.e. at exactly the same temperature as the starting lactone Ia, but showing a deep depression of the melting point when mixed with the latter (acetate of Ia, m.p. 97-98°;[5] acetate of III, m.p. 123-124°). The infra-red (1689 and 1753 cm^{-1}) and ultra-violet spectra (λ_{max} = 229 mμ, log ϵ = 3,74) of the new lactone clearly indicate the conjugation of the double bond with the carboxyl group, which suggests formulations II and III for the dihydroxy acid and the new lactone respectively. In the alkaline hydrolysis the double bond evidently shifts into conjugation.

By alkaline hydrolysis of the bromo lactone IV [1,5] we prepared the unsaturated acid Va (m.p. 183-184°; ultra-violet spectrum λ_{max} = 222 mμ, log ϵ = 3,56; found: C, 63,29; H, 5,72. $C_{11}H_{12}O_4$ requires C, 63,45; H, 5,81), resulting also from the methoxy lactone VII [1,5] by the same method. By crystallisation of the brucine salt of this acid both diastereoisomers (A, needles of m.p. 185°; $[\alpha]_D^{20}$ -17° in H_2O; found: C, 67,76; H, 6,45; N, 4,79. $C_{34}H_{38}N_2O_8$ requires C, 67,76; H, 6,36; N, 4,65; B, m.p. 147;150°, $[\alpha]_D^{20}$ -20° in H_2O; found: C, 65,71; H, 6,67; N, 4,59. $C_{34}H_{38}N_2O_8.H_2O$ requires C, 65,79; H, 6,50; N, 4,51) were obtainable and from the former the (-)-hydroxy acid Va (m.p. 165°; $[\alpha]_D^{20}$ -22° in CH_3OH; found: C, 63,21; H, 6,11; COOH, 21,18. $C_{11}H_{12}O_4$ requires C, 63,45; H, 5,81; COOH, 21,62). That this compound belongs to the reserpine series was proved

in the following way: By the action of N,N -dicyclohexylcarbodiimide in dioxane (or of acetic anhydride in pyridine) we obtained the unsaturated lactone VI (m.p. 166°; $[\alpha]_D^{20}$ -16° in $CHCl_3$; found: C, 69,38; H, 5,30. $C_{11}H_{10}O_3$ requires C, 69,46; H, 5,30), which adds one molecule of methanol in the presence of a small quantity of sodium methoxide giving the (+)-methoxy lactone VII (m.p. 99°; $[\alpha]_D^{20}$ + 49° in C_2H_5OH; found: C, 64,71; H, 6,30; CH_3O, 13,61. $C_{12}H_{14}O_4$ requires C, 64,85; H, 6,35; CH_3O, 13,86). This compound can also be prepared by methanolysis of the methylester of the acetoxy acid Vb (m.p. 90°; found: C, 63,80; H, 6,34; CH_3O, 11,57. $C_{14}H_{16}O_5$ requires C, 63,62; H, 6,10; CH_3O, 11,73).

The (+)-methoxy lactone VII is evidently identical with the substance of Velluz et al.,[2] who give the m.p. of 102° and $[\alpha]_D^{20}$ + 48° in ethanol. Our contribution thus constitutes a new and practical method of resolution during the total synthesis of reserpine.

Tetrahedron Letters, No. 5, pp. 14-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

POSSIBLE FORMATION OF TETRAPHENYLCYCLOBUTADIENE

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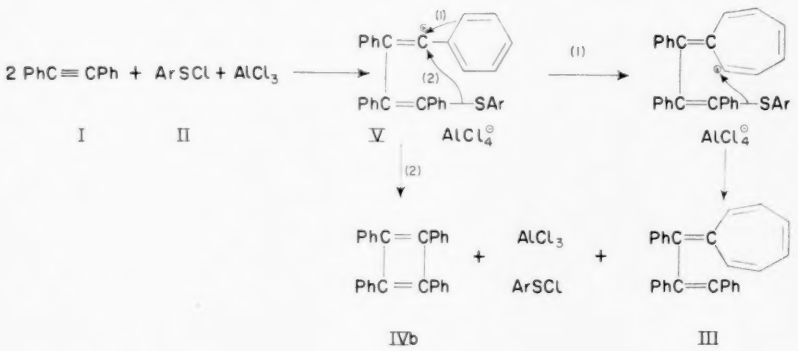
(Received 17 April 1959)

FROM the reaction between diphenylacetylene I and 2:4-dinitrobenzenesulphenyl chloride II in the presence of aluminium chloride, Assony and Kharasch isolated[1] besides the 1:1 adduct, two products with the formula $C_{28}H_{20}$: the first III was identified as 1:2:3-triphenylazulene; the second IVa, a non-identified colourless hydrocarbon melting at 154-155° formed in minute amounts, was not identical with 1:2:3-triphenylnaphthalene.

The consideration of a possible mechanism for this reaction involving



[1] S. J. Assony and N. Kharasch, J. Amer. Chem. Soc. 80, 5979 (1958).

the intermediate formation of the cation V, suggested the possibility of the colourless hydrocarbon IVa being tetraphenylcyclobutadiene IVb.

Taking into account that, as shown by Prof. C.D. Nenitzescu and collaborators in this laboratory, cyclobutadiene may be isolated as its mercury or silver nitrate complex,[2] having in gaseous state a half-life of about 1 min,[3] and that tetramethylcyclobutadiene dimerises to a unitary product,[4] it would not be surprising to find that tetraphenylcyclobutadiene is a stable compound.[5]

In view of the great theoretical importance of the cyclobutadiene problem, it would be highly interesting to test the postulated identity IVa≡IVb; the simplest method seems to be the equivalence of all four phenyl groups as shown by the nuclear (proton) magnetic resonance spectrum.[6]

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[2] M. Avram, E. Marica and C. D. Nenitzescu, Chem. Ber. 92, In press (1959).

[3] C. D. Nenitzescu, Personal communication.

[4] R. Criegee and G. Louis, Chem. Ber. 90, 417 (1957).

[5] R. Breslow and M. Battiste, Chem. & Ind. 1143 (1958).

[6] R. Breslow and C. Yuan, J. Amer. Chem. Soc. 80, 5991 (1958).

Tetrahedron Letters, No. 5, pp. 16-18, 1959. Pergamon Press Ltd. Printed in Great Britain.

EXTRAORDINARY REACTIVITY OF THE ETHYLENIC GROUP OF VINYLFERROCENE TOWARD THE ADDITION OF WEAK ACIDS

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(Received 1 May 1959)

IT has been found that vinylferrocene, prepared by the method of Arimoto and Haven,[1] possesses unusual reactivity toward electrophilic reagents, even toward such weakly electrophilic reagents as hydrogen azide and acetic acid. After treatment of 8.3 g of vinylferrocene with 166 ml of a 0.6 N hydrogen azide solution in benzene - absolute acetic acid (1:1) for 3 days at room temperature, the solution was evaporated to dryness, dissolved in Skelly B solvent and chromatographed on Alcoa alumina of reactivity grade 3. Elution with Skelly B solvent gave first 3.6 g (43%) of unreacted vinylferrocene, and, as a second fraction, 1.0 g of a liquid, n_D^{20} 1.6110, d_{25}^{25} 1.348, which was identified as 1-ferrocenylethyl azide (Calc. for $C_{12}H_{13}N_3Fe$: C, 56.50; H, 5.14; N, 16.47; Found: C, 56.77; H, 5.01; N, 16.72) by conversion to the known 1-ferrocenylethylamine[2] under conditions of catalytic hydrogenation, by preparation of the same azide in 57% yield from 1-ferrocenyl-

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[1] F. S. Arimoto and A. C. Haven, Jr., J. Amer. Chem. Soc. 77, 6295 (1955).

[2] P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson and G. M. Whitman, J. Amer. Chem. Soc. 79, 3416 (1957).

1959

ethyl alcohol by reaction with hydrogen azide under the same conditions as used in the addition of the acid to vinylferrocene, and by the presence of an infrared absorption peak in carbon disulfide solution at 4.80 μ, characteristic of the azido group. Further elution of the material on the alumina column with Skelly B-chloroform (9:1) yielded of 0.2 g of an unknown liquid (Found: C, 51.04; H, 4.51; N, 25.00; Fe, 19.93), which showed in carbon disulfide solution the presence of a strong absorption peak at 4.82 μ. A final elution with Skelly B-chloroform (4:1) afforded two additional fractions, the first of which amounted to 0.3 g and was identified as acetylferrocene. The second fraction, 3.10 g, was shown to be 1-ferrocenylethyl alcohol, formed by addition of acetic acid to the ethylenic group of vinylferrocene, followed by hydrolysis on the alumina column of the resulting acetate. In independent experiments, the alcohol was prepared in high yield by addition of acetic acid to the olefin in benzene-acetic acid (1:1) and subsequent chromatographic treatment of the product.

There is good reason to believe that the acetylferrocene obtained in the chromatographic separation arose from decomposition of 1-ferrocenylethyl azide to the corresponding imine, followed by hydrolysis of the latter compound. Whenever the pure azide is allowed to stand for some time and then re-chromatographed, acetylferrocene is obtained in addition to the azide.

The facile addition of both hydrogen azide and acetic acid to vinylferrocene appears to be without parallel in reactions of monosubstituted ethylenes. Since it is wll understood that the addition of acids to ethylenic groups proceeds by the initial addition of a proton, the results described in this Letter clearly imply that the carbonium ion Ferr-$\overset{+}{C}$H-CH_3, or a related transition ion having a protonated double bond, is formed much more rapidly than the analogous

transition ions which would have to arise from other monosubstituted ethylenes in similar addition reactions. The conclusion that the carbonium ion Ferr-$\overset{+}{C}$H-CH_3 possesses unusual stabilizing features has also been reached recently by Richards,[3] who observed that 1-ferrocenylethyl acetate undergoes rapid solvolysis in 80% acetone at 30° by the $B_{AL}1$ mechanism.

Acknowledgment — This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

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[3] J. H. Richards, Abstracts of Papers Presented at the 135th National Meeting of the American Chemical Society, Boston, April 5-10, 1959. pp. 87-90.

Tetrahedron Letters, No. 5, pp. 19-21, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE MECHANISM OF THE DIELS-ALDER REACTION

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(Received 4 May 1959)

DEWAR'S observation[1] that maleic anhydride reacts with isoprene seventy-one times faster than acrolein in anisol solution at 100° adds a potentially useful punctilio to the body of qualitative and quantitative evidence which long since showed that maleic anhydride is an exceptionally reactive participant in the Diels-Alder reaction.[2,3,4,5]

But the observation is far from providing "very strong evidence for the one-step mechanism for the Diels-Alder reaction, proceeding through a cyclic pseudo-aromatic transition state". Fortunately, recourse to subtle theoretical analysis of the question is unnecessary, since maleic anhydride is well known to be exceptionally reactive in numerous reactions which clearly involve initial attack upon one terminus of its double bond.[6] Of particular relevance

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1 M. J. S. Dewar, Tetrahedron Letters No. 4, 16 (1959).

2 M. C. Kloetzel, Organic Reactions Vol. IV, p. 1. John Wiley, New York (1948).

3 K. Alder, XIVth International Congress of Pure and Applied Chemistry, Experientia Supplementum II, p. 86. Birkhäuser, Basel (1955).

4 B. Eisler and A. Wassermann, J. Chem. Soc. 1943 (1953).

5 G. B. Kistiakowsky and J. R. Lacher, J. Amer. Chem. Soc. 58, 123 (1936).

6 L. H. Flett and W. H. Gardner, Maleic Anhydride Derivatives, Reactions of the Double Bond. John Wiley, New York (1952).

is the fact that in copolymerization experiments a terminal styryl radical reacts very much more readily with maleic anhydride than with any other monomer yet studied (including, for example, methylvinylketone, acrylonitrile, and methyl acrylate).[7,8]

We would hardly cavil at the essential distinction drawn in Dewar's succinct transliteration of a central point made in our paper on the mechanism of the Diels-Alder reaction:[9]

> "In the transition state for their isomerisation, the diene and dienophil are linked by a full bond. In the transition state for their Diels-Alder mechanism, the components are linked by a partial bond. The two transition states are quite dissimilar. It might be added that if they were not dissimilar, then the rearrangement observed by Woodward and Katz could not occur; for the transition state could equally well dissociate into two melecules of diene."

There remains the assertion, unadorned by experiment or argument:

> "Since the transition state for the rearrangement observed by Woodward and Katz is necessarily different to the transition state for the Diels-Alder reaction, the two reactions are unrelated and no conclusions concerning the mechanism of one can be drawn from that of the other."

We can only regard as bizarre, that view which holds that a process involving the cleavage of one bond of a molecule is unrelated to a process which involves the breaking of that same bond and one other. In our work it was established experimentally beyond question that the cleavage of one of the two bonds which must be broken in a particular instance of the reverse

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[7] C. Walling, Free Radicals in Solution p. 97. John Wiley, New York (1957).

[8] F. R. Mayo and C. Walling, Chem. Rev. 46, 191 (1950).

[9] R. B. Woodward and T. J. Katz, Tetrahedron 5, 70 (1959).

Diels-Alder reaction is not concerted with the breaking of the other. This demonstration provides a necessary factual basis, not hitherto accessible either from theory or experiment, for our unsymmetrical mechanism.

1959

Tetrahedron Letters, No. 5, pp. 22-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

MECHANISM OF THE BENZIDINE REARRANGEMENT

M. J. S. Dewar and Hilary McNicoll

Queen Mary College, Mile End Road, London

(Received 4 May 1959)

HAMMOND and SHINE [1] showed some years ago that the benzidine rearrangement is of second order with respect to the acid catalyst; they therefore suggested that it is the diacid salt of hydrazobenzene which rearranges. Carlin and Odioso[2] found that the order with respect to acid of the rearrangement of o-hydrazotoluene is 1.6; this they ascribed to the greater basicity of o-hydrazotoluene which leads to extensive formation of the monoacid salt under the conditions used.

However, Carlin and his collaborators[3] have also found that the rearrangements of m- and p-hydrazotoluene are of second order with respect to acid, although the basic dissociation constants of the three toluidines (K_B of o, 9.48; m, 9.26; p, 8.70) suggest that both m- and p-hydrazotoluenes should be stronger bases than the o-isomer and should therefore be converted to an even larger extent to their salts - and so show a lower

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[1] G. S. Hammond and H. J. Shine, J. Amer. Chem. Soc. 72, 220 (1950).

[2] R. B. Carlin, and R. C. Odioso, J. Amer. Chem. Soc. 76, 100 (1954).

[3a] R. B. Carlin and G. S. Wich, J. Amer. Chem. Soc. 80, 4023 (1958);
[b] R. B. Carlin and R. C. Odioso, Ibid. 76, 2345 (1954).

acid dependence.

One of us[4] has suggested an alternative interpretation of the variable acid dependency based on a mechanism involving the reversible formation of a π-complex intermediate from the monoacid salt of the hydrazobenzene, which undergoes reaction with a second proton to give the products. If this mechanism is correct, steric effects should appear in the case of hydrazobenzene derivative carrying two bulky para groups.

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We have examined the rearrangements of 4-methyl and 4-t-butyl--4'-chlorohydrazobenzene in 75 per cent alcohol, catalysed by hydrochloric acid at a constant ionic strength of 0.1. The orders of the reactions with respect to acid were:

4-methyl-4'-chlorohydrazobenzene, 1.58

4-t-butyl-4'-chlorohydrazobenzene, 1.51.

Since both these compounds must be less basic than p-hydrazotoluene, and since the t-butyl isomer should be not more basic than the methyl one, we consider these results to indicate the type of steric effect required by the π-complex mechanism. Preliminary experiments on 4:4'-bis-t-butylhydrazobenzene would also seem to indicate a steric effect.

Full details of this work and our interpretation of it will be published shortly.

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[4] M. J. S. Dewar, Bull. Soc. Chim. C67 (1951); also Kekule Symposium, London (1958).

ABSTRACTS OF SOME ACCEPTED "TETRAHEDRON" PAPERS

CONSTITUTION OF PINASTRIC ACID

P. K. GROVER and T. R. SESHADRI
Department of Chemistry, University of Delhi

Abstract—New observations in support of the revised constitution for pinastric acid based on a study of its reactions with *o*-phenylene diamine, dimethylaniline, and oxidation with sodium periodate.

STUDIES IN THE XANTHONE SERIES—IV

PREPARATION AND REACTIONS OF 2-ALLYL-L-HYDROXYXANTHONE

F. SCHEINMANN and H. SUSCHITZKY
Dept. of Chemistry and Applied Chemistry, Royal Technical College, Salford

Abstract—Preparations of furano-(II and V) and pyranoxanthones (III) from 2-allyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) and the orientation of 2-formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H) and of 4-acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac) are described. The ultra-violet absorption spectra of the new ring systems and their intermediates are briefly discussed.

TERPENOIDS—XXXIX. IRESIN (PART 5)

COMPLETE STRUCTURE AND ABSOLUTE CONFIGURATION

CARL DJERASSI AND S. BURSTEIN
Department of Chemistry, Wayne State University, Detroit, Michigan

Abstract—The remaining uncertainty in the structure of iresin (I)—the location of the angular methyl group—has now been settled rigorously by comparing the course of tribromination–dehydrobromination experiments of its derived nor-ketone XI with steroid models. Thus it was shown that di- or tri-bromination of 4α-methyldihydrotestosterone acetate leads to 2α,6β-dibromo-4-methyltestosterone acetate, also obtainable by dibromination of 4-methyltestosterone acetate. Rotary dispersion studies of relevant iresin and steroid model compounds demonstrate that this sesquiterpene possesses the "wrong" absolute configuration as compared to the steroids and higher terpenes.

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A list of papers to be published in future issues of "Tetrahedron"

A.K. BARUA and S. PATTABI RAMAN : Triterpenoids-X. The constitution of albigenic acid - a new triterpenoid sapogenin from Albizzia lebbeck Benth.

F. SCHEINMANN and H. SUSCHITZKY : Studies in the xanthone series - IV. Preparation and reactions of 2-allyl-1-hydroxyxanthone.

CARL DJERASSI and S. BURNSTEIN : Terpenoids - XXXIX. Iresin (Part 5). Complete structure and absolute configuration.

S.M. KUPCHAN, W.S. JOHNSON and S. RAJAGOPALAN : The configuration of cevine.

M.L. DHAR and T.R. SESHADRI : Ring isomeric change in isoflavones. Synthesis of 5,7-dimethoxy-6-hydroxyisoflavone, muningin and 5,7-dihydroxy-6-methoxyisoflavone.

J. HARLEY-MASON and A.H. LAIRD : Isolation and structure of the fluorescent substances formed in the oxidative reaction of adrenaline and noradrenaline with ethylenediamine.

KEN'ICHI TAKEDA, TOKUO KUBOTA and (in part) ARIMASA SHIMAOKA : Studies on the steroidal components of domestic plants - XIX. The structure of kogagenin, a sapogenin from Dioscorea tokora, Makino.

J.B. HENDRICKSON : Stereochemical implications in sesquiterpene biogenesis.

RYUJI TACHIKAWA : Synthesis of some isoquinoline derivatives.

R. GAY et A. HOREAU : Structure moleculaire et activite oestrogene - XVII. Comparaison des configurations absolues des acides bisdehydro-doisynolique normal et α,α-dimethyl β-ethyl allenolique physiologiquement actif.

L. van HOVE : Contribution a l'étude des alcaloides de l'holarrhéna congolensis Stapf. Structure de l'holarrhénine.

C.H. DePUY, R.W. KING and D.H. FROEMSDORF : Pyrolitic elimination of acetates: isotope effect, relative reactivity and mechanisms.

A. BOWERS, LAURA CUÉLLAR IBÁÑEZ and H.J. RINGOLD : Steroids - CXX. Synthesis of halogenated steroid hormones. New routes to 6α-fluorotestosterone and the 6α- and 6β-fluro analogs of progesterone.

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The synthesis of 6α- and 6β-fluoro Reichstein's compound "S" and 6α- and 6β-flurodesoxycorticasterone acetate.

A. BOWERS, E. DENOT, MARIA BLANCA SANCHEZ and H.J. RINGOLD : Steroids - CXXI. Synthesis of halogenated steroid hormones. 6α-Fluoro cortical hormones, a new class of powerful corticoids.

J.G. TRAYNHAM and O.S. PASCUAL : Effects of ring size on the reactions of cyclic olefins : halohydrins from methylenecycloalkanes.

R.H. MAZUR and J.A. CELLA : 16-Substituted steroids.

J. CASON, J.S. FESSENDEN and C.L. AGRE : Location of a branch in a saturated carbon chain.

R.P. GHANDI, O.P. VIG and S.M. MUKHERJI : Terpenoids - VI. A novel unambiguous synthesis of DL-arturmerone.

B. CLEVERLEY and P.P. WILLIAMS : Polymorphism in substituted barbituric acids.

M.J.S. DEWAR and VED P. KUBBA : New heteroatomic compounds - IV. The nitration and chlorination of 10-methyl-9-aza-10-boraphenanthrene.

A.J. BIRCH, A. HARRIS, R.W. RICKARDS, H. SMITH and W.B. WHALLEY : Studies in relation to biosynthesis - XXI. Rosenonolactone and gibberellic acid.

A. CHATTERJEE, S. BOSE and C. GHOSH : Rhetsine and rhetsinine. The quinazoline alkaloids of Xanthoxylum rhetsa DC.

SUKH DEV : Studies in sesquiterpenes - XVI. Zerumbone, a monocyclic sesquiterpene ketone.

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VINYLIERUNGSREAKTIONEN MIT TETRAVINYLBLEI

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(Received 13 April 1959)

1959

WIE wir bereits berichteten,[1] lasst sich Tetravinylblei (I) durch Umsetzung von $(NH_4)_2PbCl_6$ oder $PbCl_4$ mit CH_2=CHMgBr in Tetrahydrofuran herstellen. Wir haben nun gefunden, dass man I in wesentlich besserer Ausbeute erhält, wenn man $PbCl_2$ mit CH_2=CHMgCl in Tetrahydrofuran umsetzt:

$$2\ PbCl_2 + 4\ CH_2{=}CHMgCl \longrightarrow Pb(CH{=}CH_2)_4 + Pb + 4\ MgCl_2$$

Juenge und Cook[2] bearbeiteten unabhängig von uns ebenfalls dieses Gebiet und kamen zu ähnlichen Ergebnissen. Nach dieser Methode erhält man I in 85% Ausbeute. I ist eine farblose Flüssigkeit, die in Wasser beständig ist, von conc. HNO_3 dagegen explosionsartig zersetzt wird. Siedepunkt

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[1] Ludwig Maier, Angew. Chemie 71, 161 (1959).

[2] E. C. Juenge und S. E. Cook, Abstracts of Papers presented at the 135th Meeting of the American Chemical Society, Boston, April 1959, S.25M.

69 - 70°/11 mm,

n_D^{20} 1.5462 d_4^{20} 1.7882

MR_D ber: 57,83[3] MR_D gef: 55,87

Analyse $C_8H_{12}Pb$ ber: C 30.46; H 3.84; Pb 65.7;
gef: C 30.33; H 3.94; Pb 65.6;

Kharasch und Mitarb,[4] haben gezeigt, dass man durch Umsetzung von Tetraäthylblei mit PCl_3, $AsCl_3$ oder $SbCl_3$ Mono- und Diäthylchlorphosphine, -arsine und -stibine in fast quantitativer Ausbeute erhalten kann. In analoger Weise erhält man mit I die Vinylhalogenverbindungen dieser Elemente

$$Pb(CH{=}CH_2)_4 + 2\ MX_3 \xrightarrow{CCl_4} (CH_2{=}CH)_2PbX_2 + 2\ CH_2{=}CHMX_2$$

M = P, As, Sb, Bi
X = Cl, Br.

Wir führten die Vinylierungsreaktionen in Tetrachlorkohlenstoff durch, da von drei Versuchen, PCl_3 ohne Lösungsmittel mit $Pb(CH{=}CH_2)_4$ umzusetzen, zwei eine heftige Explosion verursachten.

0.1 Mol $Pb(CH{=}CH_2)_4$ und 0.2 Mol MX_3 (M = P, As, Sb, Bi; X = Cl, Br) wurden in 100 ml CCl_4 gelöst. Dann wurde die Mischung unter kräftigem Rühren 20 - 25 Stunden unter Rückfluss gekocht, vom ausgeschiedenen Divinylbleidihalogenid abfiltriert und das Filtrat fraktioniert destilliert. Die Ergebnisse sind in nachfolgender Tabelle zusammengefasst.

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[3] Bindungsrefraktionswerte nach A. I. Vogel, W. T. Cresswell und J. Leicester, J. Phys. Chem. 58, 174 (1954).

[4] M. S. Kharasch, E. von Jensen und S. Weinhouse, J. Org. Chem. 14, 429 (1949).

$Pb(CH=CH_2)_4 + MX_3$

MX_3	$CH_2=CHMX_2$	Ausbeute in %	Sdp.	Analyse ber.	Analyse gef	gramm $(CH_2=CH)_2PbX_2$ ber.	gramm $(CH_2=CH)_2PbX_2$ gef.
PCl_3	$CH_2=CHPCl_2$	65	102-104°C[5]	C 18.63 H 2.35 Cl 55.0	C 18.93 H 1.74 Cl 55.02	31.6	31.6 a)
PBr_3	$CH_2=CHPBr_2$	91.6	163-165°C	C 11.03 H 1.40 Br 73.37	C 11.37 H 1.24 Br 74.14	40.2	40 b)
$AsCl_3$	$CH_2=CHAsCl_2$	76.8	63- 64°C/38 mm	C 13.9 H 1.75 Cl 41.02	C 15.36 H 1.97 c) Cl 37.6	31.6	31.3
$AsBr_3$	$CH_2=CHAsBr_2$	86	76°C/14 mm[6]	Br 61.06	60.76	41.4	41.0
$SbCl_3$	$CH_2=CHSbCl_2$	62	58- 63°C/ 2 mm			31.7	32
$BiCl_3$	$CH_2=CHBiCl_2$	konnte nicht rein isoliert werden					

Zur Tabelle auf der vorhergehenden Seite:

a) Analyse $(CH_2=CH)_2PbCl_2$ Smp $>300^oC$ Cl ber. 20.96
gef. 20.38

b) Analyse $(CH_2=CH)_2PbBr_2$ Smp $>300^oC$ C ber. 11.40
gef. 11.30
H ber. 1.44
gef. 1.40
Br ber. 37.95
gef. 37.38

c) Wie die Analyse zeigt, ist hier auch noch etwas Divinylchlorarsin enthalten. Mono- und Divinylchlorarsin lassen sich durch fraktionierte Destillation nicht trennen (siehe Ref. 6).

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[5] (Lit: 104^oC) B. Bartocha, F. E. Brinckman, H. D. Kaesz und F. G. A. Stone, Proc. Chem. Soc. 116 (1958).

[6] (Lit: $74-76^oC/14mm$) Ludwig Maier, Dietmar Seyferth, F. G. A. Stone und Eugene G. Rochow, J. Amer. Chem. Soc. 79, 5884 (1957).

Ueber die Vinylierung von Halogenverbindungen von Elementen der dritten und sechsten Gruppe des Periodensystems mit Tetravinylblei wird an anderer Stelle berichtet werden.

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INTERCONVERSION OF SOME PENTYLBENZENES BY ALUMINUM CHLORIDE

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AS a continuation of our study of alkylbenzenes we have examined the behavior of several pentylbenzenes in the presence of aluminum chloride.

Recently Nenitzescu and co-workers published an account of experiments quite similar to ours.[1] Their observation of the conversion of sec-butylbenzene into isobutylbenzene was in agreement with our own[2] but, owing to the qualitative nature of their analysis, they were unaware of the reversibility of this rearrangement. These workers also reported the conversion of t-pentylbenzene into 2-methyl-3-phenylbutane, and of the latter into neopentylbenzene by more extended treatment with aluminum chloride. We now wish to report the results of a quantitative study of the reaction of these three pentylbenzenes with aluminum chloride and to explain the relationship between them in terms of a mechanism which correlates this system with the rearrangements of propyl- and

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[1] C. D. Nenitzescu, I. Necsoiu, A. Glatz and M. Zalman, Chem. Ber. 92, 10 (1959).

[2] R. M. Roberts, Y. W. Han, C. H. Schmid and D. A. Davis, J. Amer. Chem. Soc. 81, 640 (1959).

Interconversion of some pentylbenzenes by aluminum chloride

butylbenzenes.

Analysis of the pentylbenzenes after treatment with aluminum chloride was made by means of infrared spectrometry and vapor chromatography. The pentylbenzene fraction was previously separated from lower- and higher-boiling material by fractional distillation.

t-Pentylbenzene was first treated (100°, 1 hr) with water-activated aluminum chloride in the proportion used with sec- and isobutylbenzene.[2] The pentylbenzenes recovered were neopentylbenzene (65%), 2-methyl-3-phenylbutane (30%) and t-pentylbenzene (5%).[3] After milder treatment

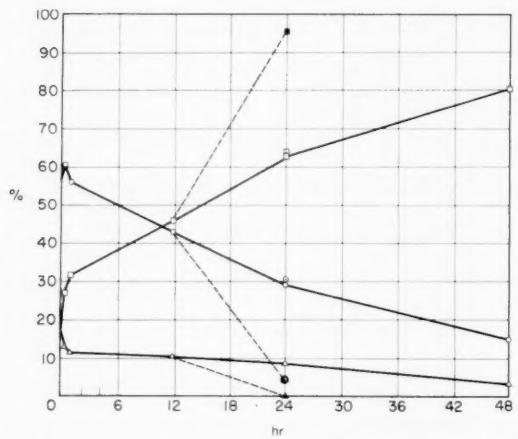
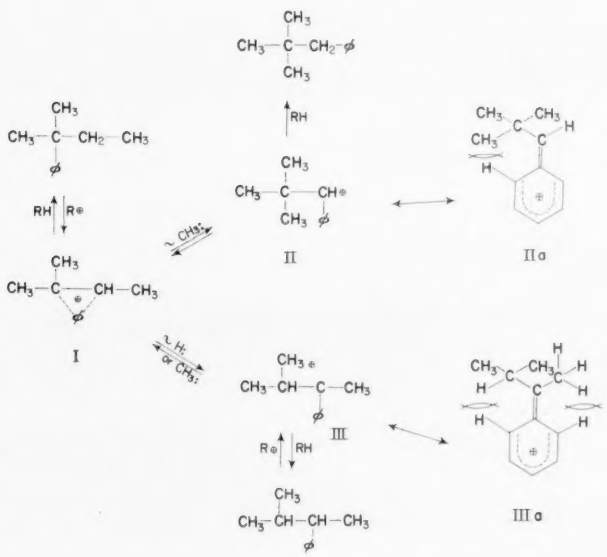


FIG. 1. Pentylbenzenes from Treatment with $AlCl_3 + H_2O$ in Benzene at 80° of
(a) *t*-Pentylbenzene: △ = *t*-pentylbenzene □ = neopentylbenzene
○ = 2-methyl-3-phenylbutane
▲ ● ● = products from a second 12 hr treatment with fresh catalyst
(b) 2-Methyl-3-phenylbutane: △ = *t*-pentylbenzene ○ = neopentylbenzene ◦ = 2-methyl-3-phenylbutane

[3] These three pentylbenzenes made up 95% of the distillation fraction; the other 5% consisted of the cracking products sec- and/or isobutylbenzene (these two were not separated on the vapor chromatogram) and isopropylbenzene.

(in benzene solution at ca. 80°, 0.5 hr) however, the major component of the pentylbenzenes was 2-methyl-3-phenylbutane (60%) in accordance with Nenitzescu's finding, accompanied by neopentylbenzene (27%) and t-pentylbenzene (13%). Further experiments in which t-pentylbenzene was isomerized by heating with catalyst for various periods of time are summarized in Fig. 1. At first, 2-methyl-3-phenylbutane was produced rapidly, neopentylbenzene less rapidly, but the latter isomer was slowly converted into the former as t-pentylbenzene disappeared. When 2-methyl-3-phenylbutane was the starting material, essentially the same mixture of isomers was produced after 24 hr. When neopentylbenzene was treated similarly for 24 hr it was virtually unchanged; less than 2% of 2-methyl-3-phenylbutane and about 2% of cracking products were found. No evidence of the production of any other pentylbenzenes in any of the experiments was obtained by either infrared spectrometry or vapor chromatography.

A mechanism which is consistent with these data is outlined below:



This scheme is similar to those proposed by Nenitzescu,[1] but incorporates the suggestion of Schmerling and co-workers[4] of anchimeric assistance in the abstraction of H:⊖ from t-pentylbenzene. It is directly analogous to those we have recently proposed for the rearrangements of propyl- and sec- and isobutylbenzenes.[5] In the present system, the intermediate ion III is favored over II energetically not only by the hyperconjugative effect, but also by the steric effect, since the t-butyl group causes severe steric inhibition of resonance in IIa.[6] Hence 2-methyl-3-phenylbutane is produced more rapidly than neopentylbenzene by the action of aluminum chloride on t-pentylbenzene. Although neopentylbenzene is produced more slowly, the reaction is irreversible. This must be due to the difficulty of abstracting H:⊖ from the side-chain of neopentylbenzene. The nine primary hydrogens are γ to the ring, there are no β-hydrogens, and the two α-hydrogens are shielded by a t-butyl group. One is led to draw the interesting deduction that there is a significant steric requirement for hydride abstraction, by either aluminum chloride-water complex or by a carbonium ion. It is probable that this factor is involved in the lack of rearrangement of n-butylbenzene,[7] isoamylbenzene[1] and perhaps some other alkylbenzenes.[8]

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[4] Who first described the rearrangement of t-pentylbenzene to 2-methyl-3-phenylbutane; L. Schmerling, R. W. Welch and J. P. Luvisi, J. Amer. Chem. Soc. 72, 2636 (1957); L. Schmerling and J. P. West, Ibid. 76, 1917 (1954).

[5] R. M. Roberts and J. E. Douglass, Chem. & Ind. In press (1959).

[6] G. Baddeley, J. Chadwick and H. T. Taylor, J. Chem. Soc. 2405 (1954); T. C. Van Hoek, P. E. Verkade and B. M. Wepster, Rec. Trav. Chim. 77, 559 (1958).

[7] R. M. Roberts, S. G. Brandenberger and S. G. Panayides, J. Amer. Chem. Soc. 80, 2507 (1958).

[8] We are grateful to the National Science Foundation for a grant which supported this research.

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A NEW SYNTHESIS OF FLAVONOLS

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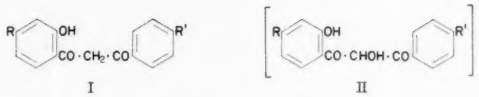
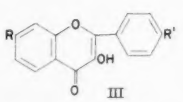
(Received 19 May 1959)

FLAVONOLS (III) are usually prepared by the Algar-Flynn-Oyamada reaction[1,2] or by the Allan-Robinson method.[3] The new synthesis here described involves the oxidation of o-hydroxydibenzoylmethanes with performic acid in chloroform. Karrer et al.[4] observed the formation of dibenzoylcarbinols



I

II



III

a=R=R'=H; b=R'=H, R=OMe; c=R=H, R'=OMe; d=R'=H, R=OBz.

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[1] J. Algar and J. P. Flynn, Proc. Roy. Irish Acad. 42B, 1 (1934).

[2] T. Oyamada, J. Chem. Soc. Japan 55, 1256 (1934); Chem. Abstr. 29, 4358 (1935).

[3] J. Allan and R. Robinson, J. Chem. Soc. 2192 (1924).

[4] P. Karrer, J. Kebrle and R. M. Thakker, Helv. Chim. Acta 33, 1711 (1950); P. Karrer, J. Kebrle and U. Albers-Schönberg, Ibid. 34, 1014 (1951); Idem, Ibid. 35, 1498 (1952).

when dibenzolmethanes in chloroform were treated with perbenzoic acid. More recently House and Gannon[5] reported the α-hydroxylation of alkan-β-diones by monoperphthalic acid in ether.

In our experiments the o-hydroxydibenzoylmethanes (I, a, b, c, d) were shaken overnight with chloroform and performic acid. Removal of the solvent under reduced pressure yielded the corresponding flavonols (III, a, b, c, d) in yields of 20 - 50%. The intermediate dibenzoylcarbinols (II, a, b, c, d) were not isolated.

This new reaction provides an acceptable route to flavonols, since dibenzoylmethanes are readily available by Baker-Venkataraman transformation[6] of the corresponding o-aroyloxyacetophenones.

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[5] H. O. House and W. F. Gannon, J. Org. Chem. 23, 879 (1958).

[6] W. Baker, J. Chem. Soc. 1381 (1933); H. S. Mahal and K. Venkataraman, Curr. Sci. 2, 214 (1933); J. Chem. Soc. 1767 (1934); B. G. Doyle, F. Gogan, J. E. Gowan, J. Keane and T. S. Wheeler, Sci. Proc. R. Dublin Soc. 24, 291 (1948).

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ADDITION OF TELLURIUM COMPOUNDS TO DOUBLE BONDS

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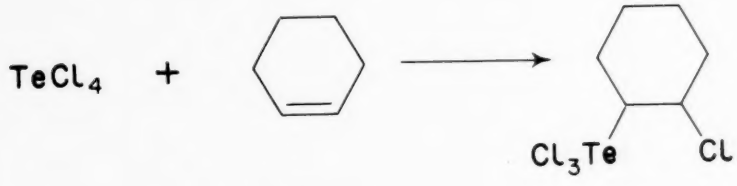
(Received 19 May 1959)

WE have found that tellurium compounds undergo addition reactions with unsaturated compounds thus representing a new type of electrophilic reagents for double bonds.

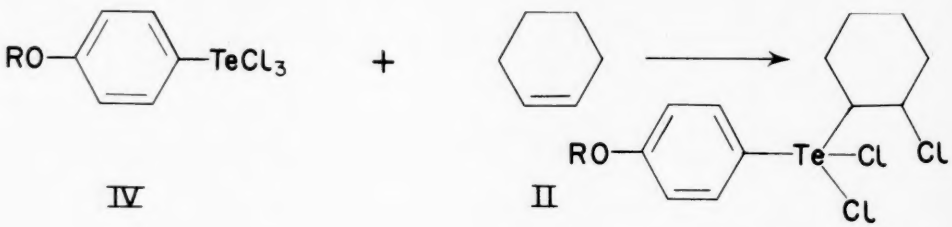
Tellurium tetrachloride (I) reacts violently with cyclohexene giving a well crystallized compound, whose analysis showed it to be 2-chlorocyclohexyl tellurium trichloride (III) [m.p. 111-114° (with decomposition); Found: Te, 36.08; $C_6H_{10}TeCl_4$ requires Te, 36.29].



I II III

When this reaction is done under carbon tetrachloride it proceeds smoothly and the yield is increased.

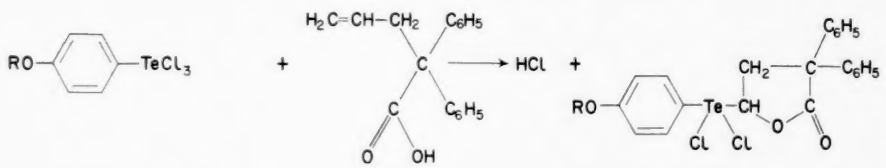
p-Ethoxyphenyl tellurium trichloride[1] (IV: R = C_2H_5) does not react at room temperature with cyclohexene, the starting material being recovered unchanged. However, when the reaction is performed with boiling cyclohexene a solid residue of p-ethoxyphenyl-2-chloro cyclohexyl tellurium dichloride (V: R = C_2H_5) is obtained, which after crystallization from ethanol melts at 97-98°.



IV II V

(m.p. 97-98°; Found: Te, 29.32; $C_{14}H_{19}OTeCl_3$ requires Te, 29.18).

When the double is activated by the participation of a carboxyl neighbouring group[2] the reaction can be performed at normal temperature.



IV VI VII

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[1] G. T. Morgan and H. D. K. Drew, J. Chem. Soc. 2307 (1925).

[2] R. T. Arnold and K. L. Lindsay, J. Amer. Chem. Soc. 75, 1048 (1953); R. T. Arnold, M.de Moura Campos and K. L. Lindsay, Ibid. 75, 1044 (1953).

Thus 2,2-diphenyl-penten-4-oic acid (VI) and compound (IV: R = CH_3[3] or C_2H_5) yield the correspondent 2,2-diphenyl-5-(p-alcoxyphenyl-dichloro tellurium)-4-pentano lactone (VII). (VII (R = CH_3) m.p. 178-181°; Found: Te, 22.89; $C_{24}H_{22}O_3TeCl_2$ requires Te, 22.91 and VII (R = C_2H_5) m.p. 193-196°; Found: Te, 21.85; $C_{25}H_{24}O_3TeCl_2$ requires Te, 22.35).

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Other tellurium compounds are also being tried out and the results of these experiments will be reported later.

Analogous compounds of type (VII) having a sulphur atom instead of tellurium have been obtained[4] and preparation of similar compounds with selenium in the molecule is in progress.

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[3] R. T. Morgan and R. E. Kellet, J. Chem. Soc. 1080 (1926).

[4] M.de Moura Campos, J. Amer. Chem. Soc. 76, 4480 (1954).

Tetrahedron Letters, No. 6, pp. 14-19, 1959. Pergamon Press Ltd. Printed in Great Britain.

TERPENES XII. THE CONSTITUTIONS OF AROMADENDRENE, GLOBULOL, LEDOL AND VIRIDOFLOROL.

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(Received 11 May 1959)

CHEMICAL investigations aimed at structure elucidation of aromadendrene produced seven formulas. The last two proposals[1] (I and II) rest on these facts. Aromadendrene contains part structure IV, dehydrogenation gives guaiazulene (III), three rings are present, one of which is probably three membered. We now wish to propose IX as the complete expression for this sesquiterpene.

We have confirmed IV by base catalyzed deuterium exchange with X (2.9D introduced) and extended it to V by exchange with VI[1] (3.0D introduced). The presence of a $C_6 \longrightarrow C_{11}$ bond was then established. Acid isomerization of dihydroaromadendrene gave XI (I.R. bands at 885, 1640, 3330 cm^{-1}) which on dehydrogenation over palladium at 320° yielded zierazulene (XIV)[2] identified by visible spectrum, picrate m.p. 116-118°,

[1] A. J. Birch and F. N. Lahey, Aust. J. Chem. 6, 379 (1953) and earlier literature cited.

[2] D. J. Collins, J. Chem. Soc. 531 (1959), whom we thank for a specimen.

trinitrobenzene adduct m.p. 119-123°, pure and mixed with an authentic sample.[2] Ozonization of XI yielded XII (ν1692 cm^{-1}), 3.0D atoms introduced with NaOD/EtOD which had mass peaks at m/e 208 (parent), 165 and 43 (CH_3CO). The diketone XIII[3] exhibited peaks at m/e 208, 165 and 43, while the hexadeuterio diketone had peaks at m/e 214, 168 and 46 (CD_3CO). This shows that XII and XIII are C_6 substituted methylketones rather than cyclooctanones.[1] Enolization towards C_6 is sterically prohibited by the methyl group at C_4 and the situation is entirely analogous to that in maaliol.[4] Since the $C_6 \longrightarrow C_7$ and $C_7 \longrightarrow C_{11}$ bonds are retained in the dehydrogenation products III and XIV, the presence of a cyclopropane ring is established.

In agreement with recent findings of Šorm and coworkers[5] ozonization of aromadendrene $[\alpha]_D^{25}$ + 7° (ethanol) from Eucalyptus Nova Anglica has repeatedly yielded only apoaromadendrone (X). Contrary to previous views,[1,6] we believe the A/B rings to be trans-locked in this ketone for the following reasons. (a) Earlier work established the higher stability of the trans-isomer in the unsubstituted bicyclo-[5.3.0]-decane system[7-9] and there is no reason to assume that the substituents present in X should

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[3] W. Treibs and H. Barchet, Ann. 566, 89 (1950).

[4] G. Büchi, M. Schach v. Wittenau and D. M. White, J. Amer. Chem. Soc. 81, 1968 (1959).

[5] L. Dolejs, V. Herout, O. Motl, F. Šorm and M. Soucek, Chem. & Ind. 566 (1959).

[6] L. Dolejs, F. Sorm and M. Soucek, Chem. & Ind. 160 (1959).

[7] D. C. Ayres and R. A. Raphael, J. Chem. Soc. 1779 (1958).

[8] H. L. Goering, A. C. Olson and H. H. Esby, J. Amer. Chem. Soc. 78, 5371 (1956).

[9] A. C. Cope and G. Holzman, J. Amer. Chem. Soc. 72, 3062 (1950).

revert this order of stability. (b) In agreement with the molecular model, the catalytic reduction of XV, m.p. 43°, λ_{max}^{EtOH} 248 mμ, ε6000; I.R. bands at 1670, 1605 (s) cm^{-1}, one vinyl hydrogen in the NMR spectrum, gave only the thermodynamically less stable α-apoaromadendrone[1] (VIII). The unsaturated ketone (XV) was readily available by bromination of X with N-bromosuccinimide followed by dehydrobromination with dimethylformamide in the presence of lithium chloride. Exposure of the ketoacid (VI) to strong alkali and treatment with hydroxylamine produced the original oximinoacid[1] which demonstrated that the large groups at C_4 and C_5 are trans. The optical rotatory dispersion curve (kindly measured by Prof. Carl Djerassi) of the cis-ketone (VIII) exhibited a single positive Cotton effect while the trans-ketone (X) had a negative curve. This relationship is in agreement with the Moffitt-Woodward octant rule[10] only if the two ketones have the absolute configurations implied in VIII and X. The configurations at the remaining centers C_6 and C_7 must be identical and the acid catalyzed ring cleavages (cf.4) already discussed strongly suggest the stereochemistry pictured in VII to XIII.

The Czech investigators have recently[5] demonstrated the existence of two diastereomeric aromadendrenes and they were able to correlate ledol[11] and viridoflorol[12] with alloaromadendrene $[\alpha]_D^{20}$ -21.6° for which

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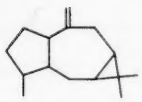
[10] R. B. Woodward, private communication.

[11] N. P. Kiryalov, Chem. Abstr. 49, 5389 (1955) and earlier papers.

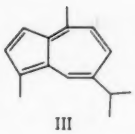
[12] R. O. Hellyer and H. H. G. McKern, J. Proc. R. Soc. N.S.W. 89, 188 (1956).

1959

I



II



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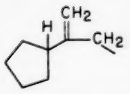

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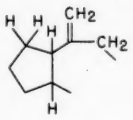
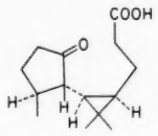
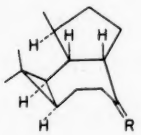


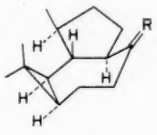
V



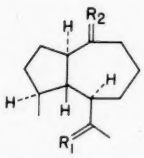
VI



VII R=CH_2
VIII R=O=



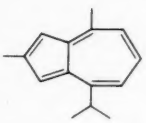
IX R=CH_2
X R=O=



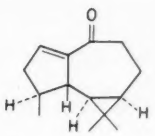
XI R_1=CH_2; R_2 = $\langle^{CH_3}_{H}$

XII R_1=O=; R_2 = $\langle^{CH_3}_{H}$

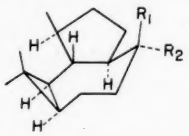
XIII R_1=O=; R_2=O=



XIV

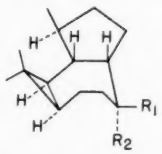


XV



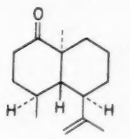
XVI R_1=CH_3; R_2=OH

XVII R_1=OH; R_2=CH_3



XVIII R_1=CH_3; R_2=OH

X!X R_1=OH; R_2=CH_3



XX

we wish to propose structure VII. Similarly, globulol[13] was obtained by partial synthesis from aromadendrene. We have independently reached the same conclusions in the following manner. Configurationally pure aromadendrene (IX) $[\alpha]_D^{25}$ +9° (EtOH) was prepared from apoaromadendrone (X) according to Wittig.[14] Epoxidation followed by reduction with lithium aluminum hydride gave globulol, m.p. 87°, $[\alpha]_D^{26}$ -43° ($CHCl_3$), phenylurethane, m.p. 144°, and a liquid tertiary alcohol $[\alpha]_D^{25}$ -34° (EtOH) possibly identical with palustrol.[15] Treatment of X with methyllithium gave only the liquid alcohol which shows[4] that this epimer has structure XVII while globulol is XVI. The configuration at C_{10} of globulol is in agreement with its behaviour on rate controlled dehydration with thionyl chloride in pyridine which provided mainly the olefin containing an exocyclic double bond.[6] Further support for the configurations assigned was provided by the mass spectra of the two epimeric alcohols. The intensity of the molecular ion at m/e 222 was 0.19% of the total ion yield in globulol while it was 0.29% in the spectrum of the epimer which indicated that globulol (XVI) is the thermodynamically less stable isomer.[16] Treatment of α-apoaromadendrone (VIII) with methyllithium gave only ledol identical by m.p., mixed m.p., rotation and infrared spectrum with an authentic sample.[17] The mode

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[13] A. Blumann, A. R. H. Cole, K. J. L. Thierberg and D. E. White, Chem. & Ind. 1426 (1954).

[14] G. Wittig, Angew. Chem. 68, 505 (1956).

[15] N. P. Kiryalov, J. Gen. Chem. U.S.S.R. 24, 1257 (1954).

[16] K. Biemann and J. Seibl, J. Amer. Chem. Soc. in press.

[17] We are indebted to Drs. P. de Mayo and T. Bruun for a sample of ledol.

of formation[4] and its behaviour on dehydration[6] indicate structure XVIII for ledol and the unsaturated ketone[11] formed on acid catalyzed dehydration of ledglycol must be XX. A configurationally homogeneous sample of alloaromadendrene (VII) $[\alpha]_D^{26}$ -19° (EtOH) was prepared by a Wittig reaction[14] from α-apoaromadendrone (VIII). Epoxidation followed by hydride reduction yielded ledol (XVIII) and an isomeric tertiary alcohol which according to Dolejs et al.[5] is identical with viridoflorol to which we assign structure XIX.

1959

We are indebted to Firmenich and Co., Geneva, for generous financial support and to Drs. K. Biemann and J. Seibl, M. I. T., for the mass spectra and their interpretation.

Tetrahedron Letters No. 6, pp.20-21, 1959. Pergamon Press Ltd. Printed in Great Britain.

GAS CHROMATOGRAPHIC EVIDENCE FOR INTRAMOLECULAR HYDROGEN BONDING WITH DOUBLE BONDS

C. H. DePuy and P. R. Story

Department of Chemistry, Iowa State College, Ames, Iowa

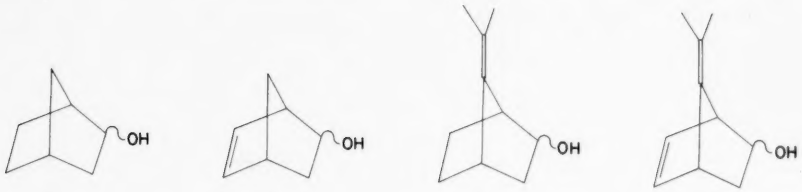
(Received 31 March 1959)

IN recent publications it has been shown that intramolecular hydrogen bonds between hydroxyl groups and carbon-carbon double bonds may be detected by infrared spectra.[1] We wish to report data which show that unsaturated bicyclic alcohols which are capable of internal hydrogen bonding show strikingly shorter retention times than epimers or dihydro derivatives which cannot so interact.

Analysis of the data in Table 1 shows that exo and endo norborneol (I) have similar retention times. Introduction of a double bond into the exo isomer has practically no effect on the retention time. Introduction of a double bond into the endo isomer (to give endo-II, the only member of the series capable of intramolecular hydrogen bonding[1c]) sharply decreases its retention time.

[1a] D. S. Trifan, J. L. Weinmann and L. P. Kuhn, J. Amer. Chem. Soc. 79, 6555 (1957); [b] A. W. Baker and A. T. Shulgin, Ibid. 80, 5358 (1958); [c] P. von R. Schleyer, D. S. Trifan and R. Bacskai, Ibid. 80, 6691 (1958).

Table 1. GLPC Retention Times[a]



	I	II	III	IV
endo	104[b]	79[b]	38[c]	30[c]
exo	96	94	28	33

[a] Retention times in minutes determined on a 12 ft x $\frac{1}{4}$ in. column packed with 23% by weight Ucon No. 50HB 2000, available from Union Carbide, on Celite.
[b] At 160° and 30 mL/min of He.
[c] At 210° and 41 mL/min of He.

Exo and endo-7-isopropylidene-dehydronorborneol (IV),[2] in both of which intramolecular hydrogen bonding may reasonably be assumed, have similar retention times. Reduction of the 5,6-double bond in the exo isomer results in a decrease in retention time. Removal of this same double bond in the endo isomer (to give endo-III, the only member of the series incapable of intramolecular hydrogen bonding) results in an increase in retention time. The net effect of intramolecular hydrogen bonding is to decrease the retention time by nearly $\frac{1}{3}$.

These observations constitute the first nonspectral evidence for such intramolecular hydrogen bonding and suggest that GLPC will be an important adjunct to I.R. in the determination of the configurations of unsaturated alcohols.

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[2] C. H. DePuy and P. R. Story, submitted to J. Amer. Chem. Soc.

Tetrahedron Letters No. 6, pp.22-25, 1959. Pergamon Press Ltd. Printed in Great Britain.

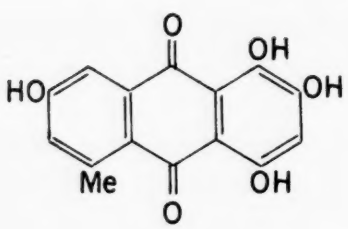
THE CONSTITUTION OF ERYTHROLACCIN

K. G. Dave, B. S. Joshi, A. V. Patwardhan and K. Venkataraman

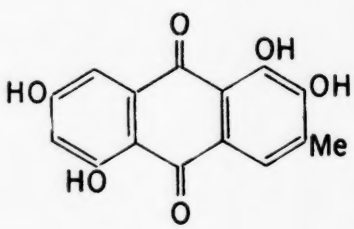
National Chemical Laboratory, Poona

(Received 22 May 1959)

TSCHIRCH and Lüdy[1] isolated from stick-lac a yellow pigment, $C_{15}H_{10}O_6$, which had the " entire behaviour of a tetrahydroxymethylanthraquinone of the tentative structure (I)". It was stated that the positions of the methyl and hydroxyl groups were still to be determined and that the suggested orientation was in view of the relationship to kermesic acid and carminic acid. The only derivative prepared was a tetra-acetate, and no melting point was cited for erythrolaccin or the tetra-acetate.



I



II

[1] A. Tschirch and F. Lüdy, Helv. Chim. Acta 6, 994 (1923).

By a slight modification of Tschirch and Lüdy's procedure we have isolated erythrolaccin as orange needles, m.p. 314° (dec.). The elementary analysis and molecular weight (Rast) corresponded to $C_{15}H_{10}O_6$. Kuhn-Roth oxidation indicated one C-methyl group. Zinc dust distillation yielded 2-methylanthracene. A tetra-acetate, m.p. 178°, and a tetramethyl ether, m.p. 150°, were obtained, the latter by means of dimethyl sulphate and potassium carbonate in acetone. Erythrolaccin is therefore a tetrahydroxy-2-methylanthraquinone. Two hydroxyl groups are in α- and two in β-positions, because methylation with ethereal diazomethane gave a dimethyl ether, m.p. 224°, which yielded a diacetate, m.p. 199°. Erythrolaccin is an alizarin derivative as shown by the shades obtained on mordanted wool; and it is not a quinizarin derivative since a solution in glacial acetic acid is non-fluorescent. The infra-red spectra of erythrolaccin and its dimethyl ether have strong absorption bands at 1617 and 1614 cm^{-1} respectively (chelated carbonyl), and none around 1672 cm^{-1} (unchelated carbonyl); the two α-hydroxyls in erythrolaccin are therefore in the 1,5 and not in the 1,8-positions. Three hydroxyl groups in erythrolaccin are thus in the 1,2,5-positions. Unlike anthragallol erythrolaccin did not give the Bargellini test, excluding the presence of three hydroxyls in 1,2,3-positions. We have shown earlier that xanthopurpurin undergoes hydroxymethylation readily in the 2-position by treatment with aqueous sodium hydroxide and formaldehyde, and have used the method for the synthesis of lucidin[2] and 1,3,8-trihydroxy-2-hydroxy-

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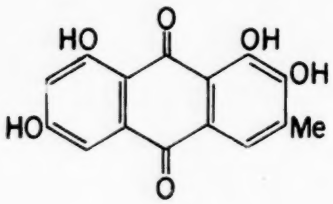
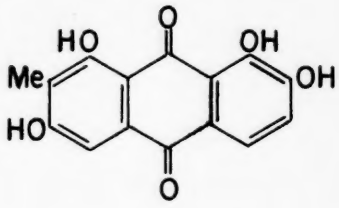
[2] N. R. Ayyangar and K. Venkataraman, J. Sci. Ind. Res. B15, 359 (1956).

methylanthraquinone.[3] We have now found that the reaction is a useful diagnostic test for the presence of two hydroxyl groups in 1,3-positions and the absence of a substituent in the 2-position. Erythrolaccin condensed readily with alkaline formaldehyde to form a hydroxymethyl derivative (dec. $>360^{\circ}$), proving simultaneously that the fourth hydroxyl group in erythrolaccin is in the 7-position and the methyl group is in the 3-position. Only one possibility, 1,2,5,7-tetrahydroxy-3-methylanthraquinone (II), therefore remains for the structure of erythrolaccin.



III



IV

Briggs et al.[4] isolated from the bark of Rhamnus alaternus a pigment, for which the trivial name alaternin may be suggested, and to which they assigned the structure 1,2,6,8-tetrahydroxy-3-methylanthraquinone (III); the chemical and spectral evidence equally supported an alternative (IV) with the methyl group in the 7-position, but (III) was preferred on

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[3] N. R. Ayyangar, B. S. Joshi and K. Venkataraman, Tetrahedron 6, In press (1959).

[4] L. H. Briggs, F. E. Jacombs and G. A. Nicholls, J. Chem. Soc. 3069 (1953).

"phytochemical grounds" as a derivative of emodin, the major colouring matter of the plant. Further support for (III) is provided by the fact that alaternin, a small sample of which was sent to us by Professor L. H. Briggs to whom we are greatly indebted, condensed readily with alkaline formaldehyde, although the quantity at our disposal was too small for characterization of the product. The synthesis of (II) and (III) is in progress.

1959

Our thanks are due to the Indian Lac Cess Committee for a Senior Research Fellowship awarded to one of us (K. G. D.) and to the Ministry of Education for a Junior Research Fellowship awarded to one of us (A. V. P.).

Tetrahedron Letters No. 6, pp.26-27, 1959. Pergamon Press Ltd. Printed in Great Britain.

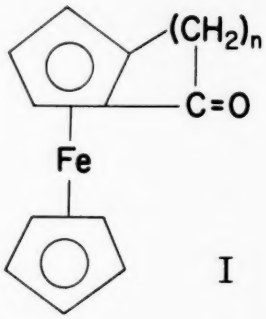
MOLECULAR ASYMMETRY IN THE FERROCENE SERIES

J. B. Thomson[1]

Chemistry Department, University College, Dublin

(Received 26 May 1959)

HOMOANNULAR disubstituted ferrocene derivatives in which the substituents differ are non-superposable on their mirror images and are therefore potentially resolvable. Representatives of this simplest type of asymmetric molecule in the ferrocene series have only recently become available[2] but



I

the closely related cyclized compounds (I) have been known for several years[3]. Optical activity in this latter type of compound has now been

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[1] I. C. I. Fellow.

[2] D. Lednicer and C. R. Hauser, J. Org. Chem. 24, 43 (1959).

[3] K. L. Rinehart and R. J. Curby, J. Amer. Chem. Soc. 79, 3290 (1957).

demonstrated.

Treatment of the ketone (I; $\underline{n} = 3$) (250 mg) with (-)-menthydrazide according to Woodward *et al.*[4] gave orange crystals of the (+)-ketone-(-)-menthydrazone (80 mg), m.p. 195-196° (vacuum sealed tube); $[\alpha]_D^{15^\circ}$ + 850° ± 5° (*c*, 0.3 in $CHCl_3$) (Found: C, 66.8; H, 7.8; N, 6.7. $C_{25}H_{34}FeN_2O_2$ requires: C, 66.7; H, 7.6; N, 6.2%). The mother liquors from the reaction mixture yielded a small amount (12 mg) of impure (-)-ketone-(-)-menthydrazone, m.p. 193-196° (vacuum sealed tube); $[\alpha]_D^{15^\circ}$ - 350° (*c*, 0.35 in $CHCl_3$). Acid hydrolysis[4] of the (+)-ketone-(-)-menthydrazone (60 mg) followed by chromatography on alumina and repeated sublimation of the product at 110-120°/2mm gave the (+)-ketone (8 mg), m.p. 83-85° (lit.[3] racemate m.p. 85.4-85.7°); $[\alpha]_D^{15^\circ}$ + 550° (still increasing) (*c*, 0.3 in $CHCl_3$) (Found: C, 66.5; H, 5.9. Calc. for $C_{14}H_{14}FeO$: C, 66.2; H, 5.6%).

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[4] R. B. Woodward, T. P. Kohman and G. C. Harris, J. Amer. Chem. Soc. 63, 120 (1941).

A list of papers recently accepted for publication in "Tetrahedron"

F. W. LAMPE and F. H. FIELD : Reactions of ions with molecules in the gas phase.

TOMOKICHIRO FUJISAWA and SHIGEHIKO SUGASAWA : Extension of the Bischler-Napieralski reaction-IV. Synthesis of some pyridine derivatives.

V. GALÍK, F. PETRŮ und J. KUTHAN : Zur Konstitution der Sandarakopimarsäure-II. Über die sterische Beziehung der Sandarakopimarsäure zu den Dextropimarsäuren.

P. C. J. BRUNET and P. W. KENT : The occurrence of protocatechuic acid and its 4-O-β-D-glucoside in Blatta and Periplaneta.

L. H. BRIGGS, R. C. CAMBIE and J. L. HOARE : Chemistry of the podocarpaceae-III. A new lignan, seco-isolariciresinol and further constituents of the heartwood of Podocarpus spicatus.

EIJI OCHIAI und MASAYUKI ISHIKAWA : Synthese von Derivaten der Cinchona-Alkaloide-XXXII. Synthese von Dihydrocorynanthean und 3-Epidihydrocorynanthean aus Cinchonin.

W. COCKER and T. B. H. McMURRY : Stereochemical relationship in the eudesmane (selinane) group of sesquiterpenes.

C. C. LEE, R. TKACHUK and G. P. SLATER : Rearrangement studies with ^{14}C-VIII. External and internal returns in the solvolysis of 2-phenyl-1-^{14}C-ethyl p-toluenesulfonate.

N. L. WENDLER, D. TAUB and R. P. GRABER : Group transfer and ring contraction phenomena in the D-homosteroid series.

A. BOWERS, E. DENOT, R. URGINZA and L. M. SANCHEZ-HIDALGO : Steroids-CXXVI. Some fission reactions of steroid 5,6-epoxides induced by boron trifluoride etherate.

A. FREGDA : Steric correlations by the quasi-racemate method.

W. COCKER, W. J. DAVIS, T. B. H. McMURRY and P. A. START : Furan tetracarboxylic acid.

U. RAMDAS NAYAK and SUKH DEV : Studies in sesquiterpenes-XVII. Hydration of longifolene.

1959

Tetrahedron Letters, No. 7, pp. 1-4, 1959. Pergamon Press Ltd. Printed in Great Britain.

ALKALOIDS FROM ASPIDOSPERMA AUSTRALE MÜLL. ARGOV.

RELATIONSHIP OF OLIVACINE TO U-ALKALOID C

Miguel A. Ondetti and Venancio Deulofeu

Laboratorios de Investigación, E. R. Squibb and Sons Argentina S. A.,

Av. Sir Alexander Fleming 1653, Martínez, Buenos Aires, Argentina

(Received 1 June 1959)

From the bark (root) of A. australe, Müll. Argov. a plant which has a wide distribution in South America, we have isolated three alkaloids identical with other bases found in A. ulei Mgf. and A. olivaceum M. Arg., both growing in the same region.

The major alkaloid (alkaloid A), is a yellow base, $C_{17}H_{14}N_2$, $(\alpha)_D^{24°} \pm 0$, m.p. 314-316° (Kofler)[1]. Ultraviolet spectrum in ethanol and ethanol-hydrochloric acid, infrared spectrum and colour reactions in exact agreement with those of olivacine, an alkaloid isolated by Schmutz and Hunziker[2] from A. olivaceum (m.p. 318-324°; $(\alpha)_D^{25°} \pm 0°$) (Found: C-CH_3: 4.80; calc. 1 C-CH_3: 6.09).

The minor alkaloids are: Alkaloid B; $C_{18}H_{20}N_2$, m.p. 243-246°; $(\alpha)_D^{29°} + 112°$ (pyridine). Ultraviolet spectrum in ethanol and ethanol-hydrochloric acid, infrared spectrum and colour reactions identical

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[1] M.p. not corrected. Analytical figures satisfactory for the isolated products and new substances.

[2] Schmutz and Hunziker, Pharm. Acta Helv. 33, 341 (1958).

with those described for u-alkaloid C, isolated from A. ulei by the same authors[3] (m.p. 249-252°; $(\alpha)_D^{25°}$ + 112°).

Alkaloid C; $C_{18}H_{22}N_2$, m.p. 78-80° (Kofler); 118-121° (Capillar); $(\alpha)_D^{25°}$ + 11.5; hydrochloride m.p. 240-241°; methiodide m.p. 204-206°. Ultraviolet spectrum m.p. and colour reactions identical with those of uleine from A. ulei[4] (m.p. 76-118°; Kofler); $(\alpha)_D^{25°}$ + 16°. (Hydrochloride m.p. 241-242°; methiodide m.p. 204-206°).

The base m.p. 314-316° (olivacine) gives a methiodide that decomposes at 320° and which was reduced with Adams' catalyst, in ethanol, to a base $C_{18}H_{20}N_2$, m.p. 223-225°. It contains one N-methyl and two C-methyl groups (Found: N-CH_3, 5.35; C-CH_3, 11.10; calc. 1 N-CH_3, 5.69; 2 C-CH_3: 11.38). This new base has colour reactions and an ultraviolet and infrared spectra in potassium bromide identical with the spectra of alkaloid B from A. australe (u-Alkaloid C from A. ulei) and appears to be the racemic form of it. This is supported by the fact that dehydrogenation of u-alkaloid C with platinum, in boiling diphenyl ether produces olivacine, identified by mixed m.p. and UV-spectrum.

The reduced base is identical with one isolated from the aerial bark of the same Aspidosperma, m.p. 223-225° $(\alpha)_D^{25°}$ ± 0° (no depression in mixed m.p.; same colour reactions, UV- and IR-spectra).

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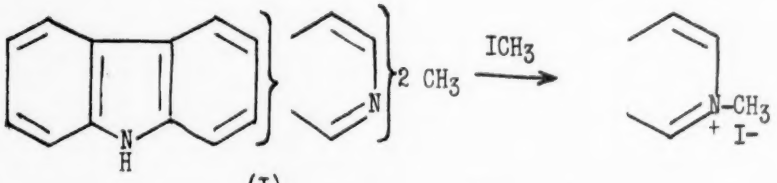
[3] Schmutz and Hunziker, Helv. Chim. Acta 41, 288 (1958).

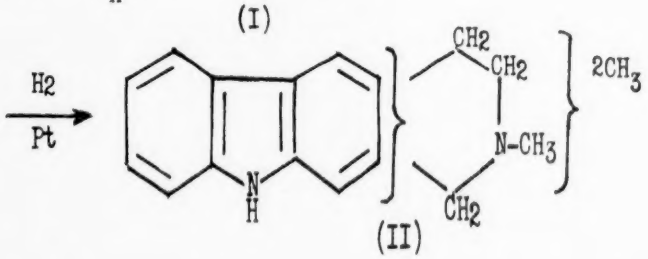
[4] Schmutz, Hunziker and Hirt, Helv. Chim. Acta 40, 1189 (1957).

The aerial bark contains also olivacine and uleine.

Schmutz and Hunziker[3] have noted that the ultraviolet spectrum of u-alkaloid C, is almost identical with the spectrum of carbazol, except that it is displaced 5-6 mμ to longer wave lengths. It does not shift on the addition of hydrochloric acid, although the maxima are increased (hyperchromic effect). These properties are exactly those of the base obtained reducing olivacine methiodide, and of alkaloid B and the inactive base m.p. 223-225° from A. australe.

The easy reduction of the methiodide of olivacine, the presence of an N-methyl group in the reduction product (II) and the carbazol spectrum of the latter, are in agreement with the hypothesis that olivacine has a carbazol unit condensed with a pyridine ring, forming an indol-quinoline or an indol-isoquinoline structure. Although the indol-quinoline structure can not be excluded, the isoquinoline (I) is more acceptable on the basis of the UV-spectrum, because in the quinoline the nitrogen of the reduced base would be directly attached to the benzene ring of carbazol, and as pointed by Schmutz and Hunziker[3] a shift in the maxima could be expected, in passing from ethanol to ethanol-hydrochloric acid, which, however, does not happen.





Because of the value obtained for C-methyl in the reduction product, two C-methyls are also present in the molecule of olivacine. At least one methyl must be a substituent of the pyridine ring to explain the optical activity of u-alkaloid C.

We thank Mr. J. F. Alicino and Dr. N. H. Coy, The Squibb Institute for Medical Research, New Brunswick, N. J., for the microanalysis and IR-spectra.

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THE PREPARATION OF N-DISUBSTITUTED FORMAMIDES

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1959

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THE conversion of primary amines to isocyanides on treatment with chloroform and base is well known and is used qualitatively to distinguish between primary and secondary amines.[1] When diethylene triamine was heated with chloroform and base, the product was found to be void of a free secondary amino group, as evidenced from the infrared spectrum. Since a literature search revealed that the reaction between a secondary amine, chloroform and base had not been investigated, a study of this reaction was initiated. Our preliminary findings indicate that secondary amines are converted to substituted formamides under the conditions of the carbylamine reaction. On refluxing dibutylamine, diisobutylamine and diethylamine with chloroform in an aqueous methanolic sodium hydroxide solution, dibutylformamide, diisobutylformamide and diethylformamide were obtained in yields of 65,35 and 40%, respectively. These amides were

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[1] J. Houben, Die Methoden der organischen Chemie Vol. 4, (3rd. Ed.) p. 587. Georg Thieme Verlag, Leipzig (1941).

identified by comparison of their physical constants with those reported in the literature.

Recently, Saunders and Murray[2] communicated a similar reaction in which secondary amines were converted to amides on treatment with chloroform and potassium t-butoxide in benzene. We are in agreement with these investigators on the course of the reaction, which might entail the following steps:

$$CHCl_3 \xrightarrow{OH^-} CCl_3^- + H_2O$$

$$CCl_3^- \longrightarrow CCl_2 + Cl^-$$

$$R_2NH + CCl_2 \longrightarrow R_2N^+HCCl_2^- \longrightarrow R_2NCHCl_2$$

$$R_2NCHCl_2 \xrightarrow{H_2O} R_2NCHO + 2HCl$$

The first two steps are well substantiated by the investigations of Hine.[3]

The following example typifies our reaction conditions:

To a solution of 129.2 g (1.0 mole) redistilled dibutylamine in 160 ml of chloroform was added a solution of 160 g (4.0 moles) of sodium hydroxide in 1 l. of methanol in 1.5 hr. The exothermic reaction caused the methanol to reflux and sodium chloride to precipitate. After the addition

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[2] M. Saunders and R. W. Murray, Tetrahedron 6, 88 (1959).

[3] J. Hine, J. Amer. Chem. Soc. 72, 2438 (1950).

was complete, the reaction mixture was refluxed for 24 hr cooled and filtered. Concentrating the filtrate and distilling in vacuo gave 19.9 g (15.40%) unreacted dibutylamine and 102.0 g (65.1%) dibutylformamide, b.p. 63° at 0.1 mm; n_D^{25} 1.4419, (lit. value[4] n_D^{25} 1.4416).

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68,69; H, 12.13; N, 8.75.

1959

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[4] H. G. Mandel and A. J. Hill, J. Amer. Chem. Soc. 76, 3978 (1954).

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KONSTITUTION DES ARENOBUFAGINS

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Pharmazeutische Anstalt der Universität Basel

(Received 1 June 1959)

ARENOBUFAGIN, das Hauptbufogenin des Paratoidensekretes der südamerikanischen Kröte Bufo arenarum Hensel, ist erstmals von Chen et al.[1] sowie von Jensen[2] isoliert und beschrieben worden. Im Laufe der Zeit haben noch eine Reihe weiterer Autoren über dieses Bufadienolid berichtet, das ausser aus B.arenarum auch aus B.mauritanicus Schlegel isoliert[3] bzw. in anderen Krötengiften mit Hilfe der Papierchromatographie nachgewiesen werden konnte.[4] Der Umstand, dass Arenobufagin auch in der chinesischen Krötengiftdroge Ch'an Su enthalten ist und daraus vor allem in Form seiner Acetylverbindung relativ leicht in reiner Form gewonnen werden kann,[5] gab uns die Möglichkeit, dieses Bufogenin abzubauen und in seiner Struktur

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[1] K. K. Chen, H. Jensen und A. L. Chen, J. Pharm. Exp. Therap. 49, 1 (1933).

[2] H. Jensen, J. Amer. Chem. Soc. 57, 1765 (1935).

[3] H. Linde und K. Meyer, Pharm. Acta Helv. 33, 327 (1958).

[4] H. Schröter, Ch. Tamm, T. Reichstein und V. Deulofeu, Helv. Chim. Acta 41, 140 (1958). Diese Arbeit enthält auch eine Literaturübersicht dieses Bufogenin betreffend.

[5] P. Hofer, H. Linde und K. Meyer, Helv. Chim. Acta (in Vorbereitung).

aufzuklären, worüber wir hier kurz berichten möchten.[6]

Die Analysenwerte für Arenobufagin und seine Acetylverbindung II passten sehr gut auf die Formel $C_{24}H_{32}O_6$ bzw. $C_{28}H_{36}O_8$, die erstmals von Deulofeu und Mitarb.[7] in Vorschlag gebracht worden sind. Das UV.-Spektrum von I zeigte das für Bufadienolide charakteristische Maximum bei 296 mμ und $\log \epsilon = 3{,}77$ (in Äthanol). Das IR.-Spektrum des freien Bufogenins wies im Bereich der HO-Bande zwei Maxima bei 2,90 - 2,92 μ und 2,98 - 3,00 μ und im Bereich der Ester-Carbonyl-Bande ein Maximum bei 5,85 μ auf, was im Vergleich zum IR.-Spektrum der Acetylverbindung (HO-Bande 2,85 μ und Carbonyl-Bande 5,80 μ mit Schulter bei 5,70 - 5,80 μ) auf das Vorliegen einer Wasserstoffbrücke im Arenobufagin hinweist.[8]

Auf Grund der Analysenergebnisse, der UV.- und IR.-Spektren und in Analogie zu den in ihrer Konstitution aufgeklärten Bufogeninen lassen sich die O-Atome in I wie folgt verteilen: 2 sind im sechsgliedrigen Lactonring enthalten, 2 liegen in acylierbaren HO-Gruppen vor, 1 ist in einer nicht oder nur sehr schwer veresterbaren HO-Gruppe gebunden und das letzte O-Atom endlich muss, wenn die Anzahl der H-Atome in den oben gegebenen Bruttoformeln für I und II korrekt ist, in einer Aldehyd- oder Ketogruppe bzw. in einer Oxidogruppe enthalten sein. Eine Aldehydgruppe konnte schon auf Grund des IR.-Spektrums von I und II ausgeschlossen werden, da die der

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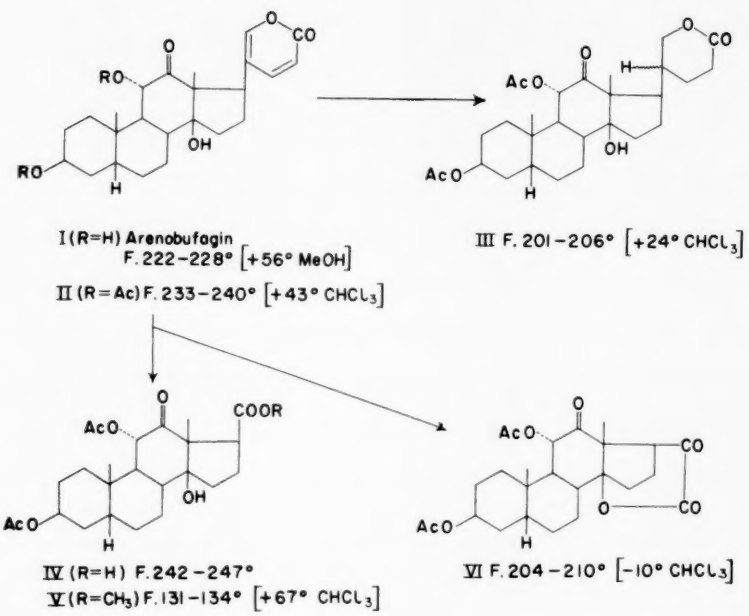
[6] Die ausführliche Arbeit erscheint demnächst in Helv. Chim. Acta.

[7] V. Deulofeu, E. Duprat und R. Labriola, Nature, Lond. 145, 671 (1940).

[8] Vergl. z.B. O. Renkonen, O. Schindler und T. Reichstein, Croatica Chem. Acta 29, 239 (1957).



I (R=H) Arenobufagin F. 222–228° [+56° MeOH]
II (R=Ac) F. 233–240° [+43° $CHCl_3$]
III F. 201–206° [+24° $CHCl_3$]
IV (R=H) F. 242–247°
V (R=CH_3) F. 131–134° [+67° $CHCl_3$]
VI F. 204–210° [–10° $CHCl_3$]

CH-Schwingung der CHO-Gruppe zukommende Bande bei 3,65 μ fehlte. Dass eine Oxidogruppe, wenn sie vorläge, nicht als Epoxyd ausgebildet sein kann, liess sich ebenfalls aus den IR.-Spektren von I und II (mit CaF_2-Prisma aufgenommen) ersehen, die bei 3,315 μ keine typische Bande zeigten.[9]

Hydrierung von II mit Pd-Kohle gab Diacetyl-tetra-hydro-arenobufagin (III), das im UV. (in Äthanol) bei 285 mμ (log ε = 1,77) selektive Absorp-

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[9] Vergl. H. Schröter, Ch. Tamm und T. Reichstein, Helv. Chim. Acta 41, 720 (1958).

tion zeigte. Da II ausserdem durch CrO_3 in Eisessig grösstenteils unverändert blieb, was einen weiteren Beweis für das Fehlen einer Aldehydgruppe darstellt, muss die in III festgestellte Carbonylfunktion, die auch für I und II gilt, durch eine Ketogruppe bedingt sein. Dies konnte noch durch den $KMnO_4$-Abbau von II einwandfrei bewiesen werden.

II wurde mit $KMnO_4$ in Aceton[10] oxydiert und gab dabei saure und neutrale Anteile. Aus den sauren Anteilen konnte die Acetoxysäure IV in Kristallen gewonnen werden. Methylierung mit ätherischem Diazomethan gab den Ester V, der sich in bezug auf Smp., Mischprobe, spez.Drehung und IR.-Spektrum als identisch mit 3β,11α-Diacetoxy-12-keto-14-hydroxy-5β, 14β-ätiansäure-methylester[8] erwies.- Aus den neutralen Anteilen der $KMnO_4$-Oxydation von II konnte ein kristallisierter Stoff der Formel $C_{25}H_{32}O_8$ gewonnen werden, dem auf Grund seines UV.-Spektrums [λ_{max} 355 mμ, log ϵ = 1,36 (in Äthanol)] [11] die Konstitutionsformel VI zukommen muss.

Arenobufagin ist somit 3β,11α-14-Trihydroxy-12-keto-5β-bufa-20, 22-dienolid.

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[10] Vergl. H. Linde und K. Meyer, Helv. Chim. Acta 42, 807 (1959).

[11] W. Schlegel, Ch. Tamm und T. Reichstein, Helv. Chim. Acta 38, 1013 (1955); St. Pataki und K. Meyer, Ibid. 38, 1631 (1955).

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STRUCTURE OF HUMULENE

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VARIOUS structures (I,[1] II,[2] III,[3] IV[4]) have been proposed for humulene. While the nature of the carbon-skeleton is well established,[5] the position of the ethylene linkages is not known with any certainty. Recently, we have demonstrated[6] that the closely related sesquiterpene ketone, zerumbone, has the structure (V). We have now examined the proton magnetic resonance (PMR) spectra of humulene, zerumbone and their hydroderivatives, and the data permit us to assign unequivocally the structure (IV) to humulene. The PMR spectrum* of zerumbone had peaks (all well-resolved) at 147.7

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1 F. Sorm, M. Streibl, J. Pliva and V. Herout, Coll. Czech. Chem. Comm. 16, 639 (1951).

2 G. R. Clemo and J. O. Harris, Chem. & Ind. 799 (1951); R. W. Fawcett and J. O. Harris, Ibid. 18 (1953); J. Chem. Soc. 2673 (1954).

3 Sukh Dev, Curr. Sci. 20, 296 (1951).

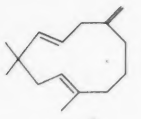
4 P. Clarke and G. R. Ramage, J. Chem. Soc. 4354 (1954).

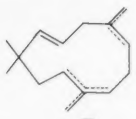
5 F. Sorm et al., Coll. Czech. Chem. Comm. 19, 570 (1954).

6 Sukh Dev, Chem. & Ind. 1051 (1956).

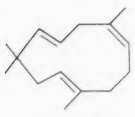
* The spectra were determined at 40 mc on 25% solutions in carbon tetrachloride, with a Varian Model V-4300B high resolution spectrophotometer. The chemical shifts were measured relative to water. The assignments for zerumbone are confirmed by the PMR spectra of tetrahydrozerumbone, hexahydrozerumbone, and humulane.

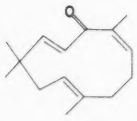
(two gem-dimethyl groups), 132.7 (one CH_3—C=C— group protons), 124.8 (second CH_3—C=C—), 104.3 (and minor peaks at 110.6 and 115.3 counts/sec; three $-CH_2-$ groups protons*), -14.2 (a triplet; one olefinic proton), and -37.9 counts/sec (two olefinic hydrogens β to the carbonyl and one olefinic proton α to the carbonyl). It should be noted here that the 'saturated' methyl groups, 'olefinic' methyl groups and the methylene


I


II

III


IV


V

groups are well-separated in a characteristic manner. The PMR spectrum of humulene** is almost identical with that of zerumbone in the methyl and methylene proton region [peaks at 152, 137.8, 128.8, and 113.2 (with a small peak at 122.2) counts/sec with the areas approximately in the ratios 2:1:1:2] and this would indicate that humulene also has four methyl groups, which is in accord with structure (IV) only. Besides these bands, humulene showed the remaining 'extra' methylene group at position 9, as expected, at a still lower field strength (peaks at 90.8 and 98.6 counts/sec with

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* These protons are well-separated from the $=C-CH_3$ peaks by virtue of all the methylene groups being allylic to the ethylenic linkages.

** Humulene was isolated from the essential oil of Zingiber zerumbet and after precise fractionation had: b.p. 114-115°/5 mm, n_D^{25} 1.5015, $[\alpha]_D^{25}$ -0.31, nitrosochloride m.p. 175-176°, trioxide m.p. 122°.

the areas approximately in the ratio 1:1 and roughly of one-third the intensity of a single methyl peak); the olefinic protons showed up as a complex group of bands, the major peaks being located at -1.0, -16.8, and -24.6 counts/sec.

According to previous workers, humulene contains one exo-cyclic $=CH_2$ group, and this contention is based on the infra-red data,[7] and $=CH_2$ group determinations involving ozonolysis.[7] Since, ozonolysis of certain systems is known to yield abnormal products, the results of $=CH_2$ group estimations do not constitute an argument against structure (IV). As for the infra-red data, we have re-examined the infra-red absorption of humulene quantitatively, and find the apparent ϵ of the relevant peaks as follows: 1665 (ϵ 20.8), 965 (ϵ 125), 885 (ϵ 32), and 820 cm^{-1} (ϵ 64). It would be clear from this data that the peak at 885 cm^{-1}, on which the presence of $=CH_2$ group had been based by these workers, is very weak,* and hence is not a forcing argument for the presence of $=CH_2$ group. Thus, the evidence presented in this paper allows the unequivocal formulation of humulene as (IV). This structure is directly related to that of zerumbone by an oxidation-reduction system, and we are currently trying to effect such transformations.

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[7] F. Sorm, J. Mleziva, Z. Arnold, and J. Pliva, Coll. Czech. Chem. Comm. 14, 699 (1949).

* The usual value of the apparent ϵ for $\nu^{C=CH_2}$ is ~40 and for $\delta^{=CH_2}$ ~115. The intensities of the other bands at 965 (one trans- -HC= CH-) and 820 cm^{-1} (two -HC=C-) are as anticipated. (R. N. Jones and C. Sandorfy in A. Weissberger's Technique of Organic Chemistry Vol. IX, pp. 367-384. Interscience, New York (1956).

A fuller acount of this work will be reported shortly in Tetrahedron.

Acknowledgement - This work was carried out at the Noyes Chemical Laboratory, University of Illinois, Urbana, and the author wishes to place on record his sincere gratitude to Professor E. J. Corey for these facilities.

1959

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THE CONFIGURATION OF (-) TROPIC ACID AND OF ITS NATURALLY OCCURRING ESTERS

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(-) TROPIC acid is the acidic building stone of a number of important alkaloids, among others of hyoscyamine and hyoscine. In order to obtain a deeper insight into the biosynthesis and mode of physiological action of the latter compounds, establishing of the absolute configuration of (-)tropic acid was required.

β-chlorohydratropic acid (II) was resolved by McKenzie and Strathern[1] more than three decades ago, and the levorotatory acid was subsequently hydrolysed to (-)tropic acid (I) the reaction being accompanied by slight racemization; hydrolysis with ammonium hydroxide gave (-)tropamide in a still higher state of optical purity.

On the other hand, (+)α-methylphenylacetic acid (IIIb) was treated by the Curtius reaction to give (-)phenylethylamine[2] (IV), and the N-benzoyl derivative was oxidized, in turn,[3] to (+) alanine (V).

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[1] A. McKenzie and R. C. Strathern, J. Chem. Soc. 127, 86 (1925).

[2] H. I. Bernstein and F. C. Whitmore, J. Amer. Chem. Soc. 61, 1324 (1939).

[3] W. Leithe, Ber. Dtsch. Chem. Ges. 64, 2827 (1931).

According to the unequivocal convention of Cahn et al.,[4] (+)α-methylphenylacetic acid is designated as S (+)α-methylphenylacetic acid (IIIb), where the R configuration corresponds to the levorotatory form (IIIa).

The single missing link between tropic acid and alanine was now the establishment of the correlation of (-)β-chlorohydratropic acid (II) with either S or R α-methylphenylacetic acid. This work has been done recently in the laboratory of the authors.

β-chlorohydratropic acid obtained from atropic acid[5] was resolved by codeine instead of morphine used by McKenzie.[1] The codeine salt of (-)β-chlorohydratropic acid melted at 138° (decomp.), $[\alpha]_D^{20}$ -95° (c = 0.4, in methanol). (Found: C, 67.9; H, 6.3; N, 2.7. $C_{27}H_{30}O_5NCl$ requires C, 67.0; H, 6.2; N, 2.9%).

The levorotatory acid, m.p. 62°, gave correct[1] rotational values, $[\alpha]_D^{20}$ -115° (c = 0.4; in 96% ethanol).

Hydrogenolysis of this compound over a Pd-charcoal catalyst in ethyl acetate in the presence of barium hydroxide resulted in the formation of R (-)α-methylphenylacetic acid, $b.p._{1-2}$=115°, $[\alpha]_D^{20}$ = -76° (c = 0.794 in 96% ethanol). (Found: C, 72.2; H, 6.7. $C_9H_{10}O_2$ requires: C, 72.0; H, 6.7%.)

The Cahn - Ingold - Prelog convention,[4] gives the unequivocal configuration of S (-)tropic acid (I) for the levorotatory form.

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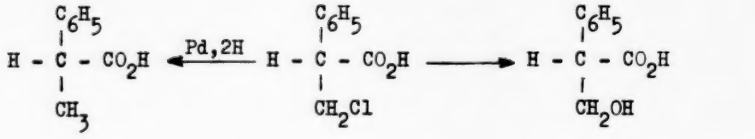
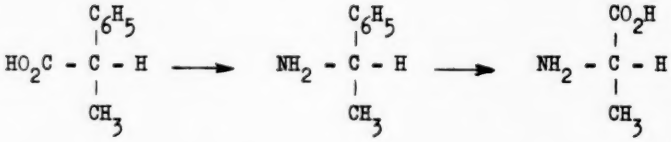
[4] R. S. Cahn, C. K. Ingold and V. Prelog, Experientia 12, 81 (1956).
[5] A. McKenzie and J. K. Wood, J. Chem. Soc. 115, 835 (1919).



IIIa (-) II (-) I (-)-Tropic acid



IIIb (+) IV (-) V (+)-Alanine

All these formulae are Fischer projection.

Accordingly, (-)hyoscyamine is S (-)tropoyl-tropan-3α-ol, and (-)hyoscine is S (-)tropoyl-3α-hydroxy-6,7 β-epoxy-tropane.

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EPOXIDATION EXPERIMENTS IN VIVO WITH DEHYDROHYOSCYAMINE AND RELATED COMPOUNDS

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(Received 11 May 1959)

A PREVIOUS paper of one of us[1] reported on the ability of overground organs of Datura ferox L. to convert hyoscyamine (I) into (-)scopolamine, i.e. hyoscine (IV). From the results of the synthesis of scopolamine[2,3] involving epoxidation of tropenyl acetate[2] and (-)tropenyl tropoylate[3] (6.7-dehydrohyoscyamine), one of us (G.F.) suggested[4,5] that the conversion of hyoscyamine into hyoscine takes the same pathway.

In order to check the correctness of this assumption feeding experiments with (-) 6.7-dehydrohyoscyamine (III) have been carried out essentially by the same technique as used for hyoscyamine.[1] Datura ferox L.

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[1] A. Romeike, Flora 143, 67 (1956).

[2] G. Fodor, J. Tóth, I. Koczor, P. Dobó and I. Vincze, Chem. & Ind. 764 (1956); J. Chem. Soc. In press (1959).

[3] G. Fodor, J. Tóth, A. Romeike, I. Vincze, P. Dobó and G. Janzsó, Angew. Chem. 69, 678 (1957).

[4] G. Fodor, Abhandl. Dtsch. Akad. Wiss. Kl. Chem. 93 (1957).

[5] G. Fodor, Tetrahedron 1, 86 (1956).

grafted[1] on Cyphomandra betacea (CAV) SENDTN, is practically void of alkaloids. Branches of half a year old Datura scions were cut (green weight 15.5 g) and placed into a $1.5.10^{-3}$ molar solution of (-) 6.7-dehydro-hyoscyamine acetate of pH 6.7.

After a week, the alkaloids were extracted and separated by paper chromatography. The fraction which showed the R_f value characteristic for hyoscine (IV) was converted into the picrate, m.p. 175°, $[\alpha]_D^{20} = -6.5°$ (c = 2; dimethyl formamide). (Found: C, 52.2; H, 5.0; N, 10.5. $C_{23}H_{24}O_{11}N_4$ requires C, 51.9; H, 4.5; N, 10.5%) identical in every respect with an authentic sample and with the compound obtained from feeding experiments with (-)hyoscyamine (Found: C, 52.0; H, 4.5; N, 10.7%).

Decisive evidence for the intermediate role of tropenyl (-)tropoylate (III) in the epoxidation of hyoscyamine was expected to be furnished by isolating 6.7-dehydrohyoscyamine after feeding of Datura ferox with hyoscyamine in the presence of oxidation inhibitors, e.g. calcium nitrate or cysteine (cf. Romeike[6]).

In this case, however, no definite ring of tropenyl tropoylate could be found with certainty on paper chromatograms, the main product being a hitherto unknown tropanol ester[6] which is also formed to a slighter extent along with hyoscine in normal epoxidations. The alkamine of this alkaloid U[6]

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[6] A. Romeike and L. Zimmerman, Naturwissenschaften 45, 187 (1958).

[7] The absolute configuration of valerine has been determined by G. Fodor, I. Vincze and J. Tóth, Experientia 13, 183 (1957).

is not identical either with tropine or with pseudotropine, teloidine, scopine or oscine. First, the structure of 3R:6R (-)dihydroxytropane 3-tropic acid ester((-)tropoyl valerine, II) had been assumed,[8] and this compound was synthesized hydrobromide m.p. 174°, $[\alpha]_D^{23} = -69^\circ$ (c = 2; in water); (Found: C, 53.6; H, 6.3; N, 3.8; Br, 20.9. $C_{17}H_{24}O_4NBr$ requires C, 52,5; H, 6.3; N, 3.6; Br, 20.7%), and compared with alkaloid U. These compounds were not identical.

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Feeding experiments with S(-) tropoyl valerine (II) under the same conditions as with dehydrohyoscyamine led again to the formation of hyoscine, while in the presence of cysteine it was converted into the alkaloid U.

In contrast to intact branches of Datura ferox on Cyphomandra, homogenized scions thereof proved to be unable to carry out epoxidation either of hyoscyamine (I) or of dehydrohyoscyamine (III). On the other hand, scions of Datura stramonium L., Datura innoxia MILL., Datura metel L., Atropa belladonna L. grafted on Cyphomandra and fed with hyoscyamine and dehydrohyoscyamine leave these compounds unaffected.

No epoxidation took place when Datura ferox on Cyphomandra was fed either with unesterified tropanols e.g. tropine, tropenol, teloidine, or with apoatropine;[8] accordingly, the action of the oxidizing enzyme in play appears to be strongly stereospecific and limited to the esters of S tropic

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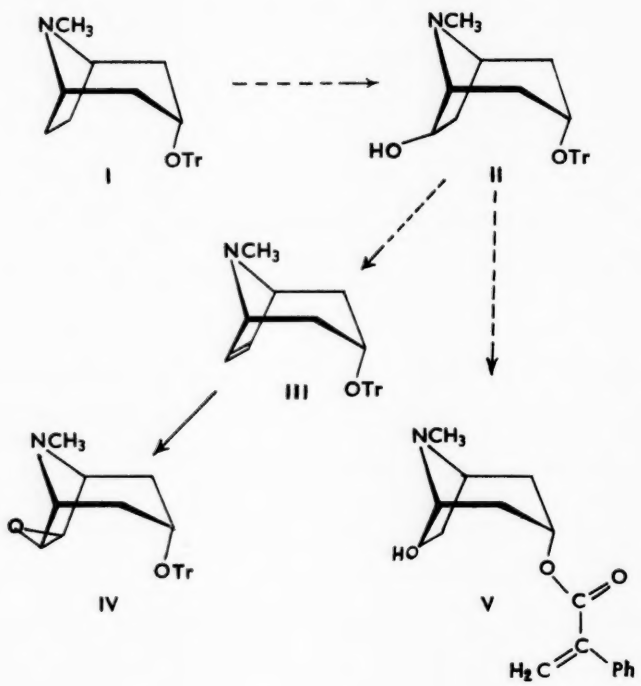
[8] G. Fodor, Lecture, Congress, 50th Anniversary of the Society of Hungarian Chemists, Budapest, May 16, 1958; G. Fodor, P. Dobó, G. Janzsó, I. Koczor, A. Romeike, J. Tóth and I. Vincze, Magy. Kém. Folyóirat 64, 296 (1958).

acid[9] with tropine, tropenol and 3R:6R -tropandiol. However, mandelyl tropine "homatropine" is epoxidized *in vivo*; the optical activity of the new epoxy-tropanium ester salt still awaits investigation to show whether the D or the L mandelyl ester (or both) is attacked.

Our present working hypothesis for the interconversion of natural tropane alkaloids *in vivo* may be depicted by the following scheme

I→II→III→IV



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[9] S configuration of (-) tropic acid has been determined recently by correlating with D (-) alanine by G. Fodor and Gy. Csepreghy, Tetrahedron Letters No. 7, 16 (1959).

Dr. Romeike suggests for alkaloid U the structure of atropoyl-3R:6R (-) dihydroxy tropane (V), regarding it as a by-product of hyoscine formation in the plant, unable to undergo epoxidation. Further investigations are in progress.

1959

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A NEW SYNTHESIS OF 1- AND 2-AMINO PHENAZINES

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(Received 19 May 1959)

THE preparation of phenazine dyes by the oxidation of mixtures of aromatic amines is assumed to take place through the intermediate formation of indamines. 2-Aminoindamines do indeed undergo ready cyclization to yield 2-aminophenazines,[1,2] probably by a similar mechanism to that involved in the ready addition of aromatic amines to quinones.[3] Although Nietski et al.[4] prepared 2-amino-, 2,7-diamino- and 2-amino-7-hydroxy-phenazine by the oxidation of 2,4'-diamino-, 2,4,4'-triamino- and 2,4'-diamino-4'-hydroxy-diphenylamine respectively with manganese dioxide, it is somewhat surprising that this type of reaction has not been more extensively used for the synthesis of simpler phenazines, particularly since it might be expected to give the products in relatively high yield in contrast to most of the available methods for phenazine synthesis.

Failure to synthesize 2-amino-6-methoxyphenazine by the oxidation of 2,4'-diamino-6-methoxydiphenylamine with inorganic reagents led us to

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[1] Ullman and Gnaedinger, Ber. Dtsch. Chem. Ges. 45, 3437 (1912).

[2] Cohen and Crabtree, J. Chem. Soc. 119, 2055 (1921).

[3] Pearson et al., Heterocyclic Compounds (Edited by Elderfield) Vol. 6, Chap. 14; John Wiley, New York (1957).

[4] Nietski et al., Ber. Dtsch. Chem. Ges. 23, 1852 (1890); 28, 2969 (1895).

attempt the reaction using organic nitro compounds as oxidizing agents. Refluxing the diphenylamine in nitrobenzene gave a 40% yield of the required phenazine (m.p. 278 - 281°; C, 69.3; H, 5.1; N, 18.3%. $C_{13}H_{11}ON_3$ requires C, 69.3; H, 4.9; N, 18.65%). The same technique applied to 2,4'-diaminodiphenylamine gave a 50-60% yield of pure 2-aminophenazine.

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Amino and methoxy groups in the 2' position are usually eliminated on oxidation of 2-aminodiphenylamines (see ref. 3). Although 2,2'-diaminodiphenylamine gave phenazine quantitatively with ferric chloride,[5] our method gave a 50% yield of 1-aminophenazine, identical with a sample prepared by Cookson's synthesis.[6]

That the reaction mechanism involves the participation of the 2' or 4' substituent is shown by the low yields of phenazines obtained when the method was applied to diphenylamines in which such substituents were lacking; e.g. 2,4-diaminodiphenylamine gave only a 5% yield of 2-aminophenazine, and 2-aminodiphenylamine only a trace of phenazine. The mechanism must therefore be different from that involved in the production of carbazole by heating 2-aminodiphenyl with organic nitro compounds.[7] A mechanism involving quinone imines as intermediates, such as that generally proposed for the oxidative cyclization of 2-amino-diphenylamines is possible but is difficult to reconcile with the production of 2-amino-8-methoxyphenazine (m.p. 217-220°; C, 68.5; H, 5.1; N, 18.35. $C_{13}H_{11}ON_3$ requires C, 69.3; H, 4.9; N, 18.65%) in 64% yield from

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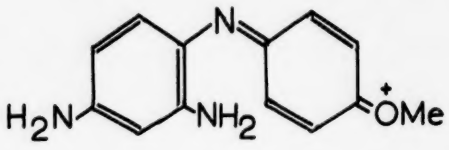
[5] Tomlinson, J. Chem. Soc. 158 (1939).

[6] Cookson, J. Chem. Soc. 1328 (1953).

[7] Weinmayr, U.S.P. 2, 351, 171 of June 13, 1944.

2,4-diamino-4'-methoxydiphenylamine unless a quinonoid cation of type I is assumed as an intermediate in the oxidation.



The 2' methoxy isomer, on the other hand, gave only a small yield of 1-aminophenazine, the elimination of the methoxy group in this instance being in marked contrast to the retention of a 2'-amino group.

It seems possible that this method can be applied generally to the synthesis of 1- and 2-aminophenazines as well as to phenazines with some other substituents in the 1- and 2-positions. These possibilities and the mechanism of the reaction are being explored and full details will be reported later.

Acknowledgements are due to the University of Cape Town for financial support and to the Council for Scientific and Industrial Research for a bursary to one of us (A.G.).

1959

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ORIENTATION IN THE REACTION OF PHENYLLITHIUM WITH 3-SUBSTITUTED PYRIDINES

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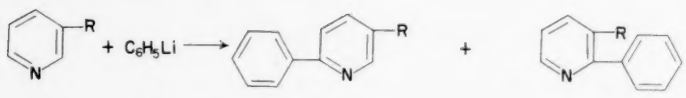
(Received 4 June 1959)

A STUDY of the addition of phenyllithium to 3-substituted pyridines was undertaken to determine the orientation of the entering phenyl group. While this work was in progress Wiley et al.[1] reported that the reaction of 3-phenylpyridine I(R = C_6H_5) with phenyllithium II was selective in giving 2,5-diphenylpyridine III(R = C_6H_5) exclusively. The formation of 2,3-diphenylpyridine IV(R = C_6H_5), which Wiley et al. regard as less probable, was not observed.



I II III IV

The addition of other nucleophilic reagents such as sodamide[2,3] and butyl-

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[1] R. H. Wiley, C. H. Jarboe, P. X. Callahan and J. T. Nielsen, J. Org. Chem. 23, 780 (1958).

[2] E. Plazek, A. Marcinikov and Ch. Stammer, Roczn. Chem. 15, 365 (1935); Chem. Abstr. 30, 1377 (1936).

[3] E. Hardegger and E. Nikles, Helv. Chim. Acta 39, 505 (1956).

lithium[4] to 3-substituted pyridines indicated the preferential formation of the 2,3-isomer in such reactions. Since our results with phenyllithium also show this trend we report some of our observations.

With 3-picoline, II gave 2-phenyl-3-picoline IV($R = CH_3$), b.p. 154-156°/18 mm, (picrate, m.p. 165-166°), and 6-phenyl-3-picoline III($R = CH_3$), b.p. 162-164°/20 mm, (picrate, m.p. 181-183°), the relative yields of IV and III being in the ratio of 8:1 respectively. The structure of the main product was proved by permanganate oxidation to 2-phenylpyridine-3-carboxylic acid IV(R = COOH), m.p. 168-169° (lit.[5] m.p. 168-169°) which was converted *via* the acid chloride into 4-azafluorenone,[6] m.p. 139.5-141.5°, by $AlCl_3$ in light petroleum. When the acid chloride was treated with $AlCl_3$ in benzene 3-benzoyl-2-phenylpyridine IV($R = C_6H_5CO$), b.p. 155-160°/15 mm, picrate, m.p. 137.5-138.5°, was obtained. The structure of 2-phenyl-3-picoline was confirmed by direct comparison with a specimen obtained unambiguously by Ishiguro *et al.*,[5] the IR spectra of the products and their picrates being identical and a mixed melting point of the picrates being undepressed. The NMR spectrum of the product was also consistent with its formulation as 2-phenyl-3-picoline. The structure of III($R = CH_3$) was similarly proved by oxidation to 2-phenylpyridine-5-carboxylic acid, m.p. 232-233° (lit.[7] m.p. 233°). A dimethyldipyridyl, characterized as the dipicrate, m.p. 204-206° (decomp.), was isolated as a byproduct of the reaction and shown to

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[4] N. J. Leonard and B. L. Ryder, J. Org. Chem. 18, 596 (1953).

[5] T. Ishiguro, Y. Morita and K. Ikushima, Yakugaku Zasshi 78, 220 (1958); Chem. Abstr. 52, 11846g (1958).

[6] Z. Skraup and A. Cobenzl, Monatsh. 4, 436 (1883), report m.p. 140-141° for 4-azafluorenone.

[7] N. Nienburg, Chem. Ber. 67, 874 (1934).

be different from 3,3'-dimethyl- and 5,5'-dimethyl-2,2'-dipyridyl by a comparison of the picrates. The structure of this byproduct was not investigated further at this stage.

In view of the results of Wiley et al.[1] the possible steric effect of the 3-substituent upon the orientation of the entering phenyl groups was investigated in the reaction of II with nicotine. The product was shown to be a 1:1 mixture of 2-phenyl- IV(R = -α-$C_4H_7NCH_3$) and 6-phenylnicotine III(R = -α-$C_4H_7NCH_3$) by vapour phase chromatography. The two isomers were separated by preparative vapour phase chromatography giving 2-phenylnicotine, b.p. 145°/0.7 mm, picrate, m.p. 211-213° and 6-phenylnicotine, b.p. 165°/0.6mm, picrate, m.p. 170-171°. The structures of the isomers were assigned on the basis of their infrared spectra (characteristic bands at 1610-1570 cm^{-1}) and by oxidation of the second fraction to 2-phenylpyridine-5-carboxylic acid.

Addition of II and of other nucleophilic reagents seems to occur preferentially at the 2-position but the 3-substituent, if sufficiently bulky, may exert a steric effect resulting in appreciable addition at the 6-position also. The exclusive formation of 2,5-diphenylpyridine[1] might be attributed to steric inhibition of coplanarity in the transition state in the formation of the 2,3-isomer.

Acknowledgements - The authors wish to thank Dr. Ishiguro for samples of 2-phenyl-3-picoline and its picrate, and Varian Associates for the NMR spectrum of 2-phenyl-3-picoline and its interpretation. This work was supported by a National Research Council of Canada grant.

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CYCLOÖCTADECANONAENE: A THEORETICAL STUDY

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(Received 1 June 1959)

THE recent report of the preparation of cycloöctadecanonaene[1] suggests that a brief discussion of the results of a simple molecular orbital calculation on this system of 18 π-electrons might be of interest. Detailed results do not seem to be available in the literature, although they can readily be obtained from the general formulae for cyclic polyenes.

The calculations were made by the standard Hückel method.[2] The energy of the N-V transition was also obtained by a perturbation method due to Dewar.[3] The results for the resonance energy, the energy of the N-V transition, the free valency, the bond order and the corresponding bond length are shown in Table 1.

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[1] F. Sondheimer and R. Wolovsky, Tetrahedron Letters No. 3, 3 (1959).

[2] C. A. Coulson and H. C. Longuet-Higgins, Proc. Roy. Soc. A 192, 16 (1947).

[3] M. J. S. Dewar, J. Chem. Soc. 3532 (1952).

TABLE 1. Molecular orbital calculations for $C_{18}H_{18}$

Method	Resonance energy (β) (kcal/mole)	Energy of N-V transition (β)	Wavelength of N-V transition (Å)	Bond order (Å)	Bond length (Å)	Free valency
Hückel	5.03 103	0.69	6030	1.640	1.404	0.452
Dewar		0.80	5200			
Expt.			4080			

The value in kcal/mole for the resonance energy is based on a value of 41 for benzene. This does not take into account compression energy. The energy per π-electron is somewhat less than in benzene, indicating that cycloöctadecanonaene is likely to be somewhat less stable than benzene. The free valency is about the same as that of the α-position in naphthalene; so there should be a similar reactivity to free radical reagents.

The bond order is the same for all the bonds, and the bond length shown in Table 1 was obtained from an empirical formula due to Longuet-Higgins and Salem.[4] On the basis of their work it seems probable that a more refined calculation would also give the result that all bonds are equal in length. The X-ray study mentioned in reference 1 should settle this question.

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[4] H. C. Longuet-Higgins and L. Salem, Proc. Roy. Soc. A 251, 172 (1959).

The reported U.V. spectrum has maxima at 4480, 4080, 3690 and 2780 Å with extinction coefficients of 21800, 7500, 303000 and 8100 respectively. These may be identified with Clar's α, p, β, and β' bands[5] respectively, giving a ratio of 1.2 for the wavelengths of the α and β bands compared to the usual ratio of 1.3. This supports the assignment of the longest wavelength transition as α rather than p. The theoretical values given in Table 1 refer to the p band, and the agreement is rather disappointing, even if the argument given above is wrong and the longest wavelength transition is in fact the p band.

A tentative assignment of the symmetries of the excited states can be made for a structure having D_{6h} symmetry by arguments similar to those used by Dewar and Longuet-Higgins.[5] The symmetries and energies of the two highest filled orbitals and the two lowest unfilled orbitals are shown in Table 2. They may be called B', A', and A, B respectively.

TABLE 2. Lowest unfilled and highest filled orbitals

Designation	Energy (β)	Symmetry
B'	-1.0000	a_{2u}, a_{1u}
A'	-0.3472	e_{1g}
A	0.3472	e_{2u}
B	1.0000	e_{1g}

[5] M. J. S. Dewar and H. C. Longuet-Higgins, Proc. Phys. Soc. A 67, 795 (1954).

1959

The first electronic transition A→A' gives rise to excited singlet states having B_{1u}, B_{2u}, and E_{1u} symmetry. Only the transition to the E_{1u} state is allowed. This may be identified with the intense band at 3690 Å. This has been called the β band above. The transition is similar to that in benzene, and by analogy the weaker bands at 4480 and 4080 Å may be identified with the forbidden transitions to the $^1B_{2u}$ and $^1B_{1u}$ states respectively. The next group of excited states involves the degenerate transitions B→A' and A→B'. These states have symmetries A_{1g}, A_{2g}, and E_{2g}, and the transitions are all forbidden. The band at 2780 Å may be identified with one of these. The next excited state involves the transition B→B', and it has E_{1u} symmetry. This transition is allowed and as the energy is still only 2β, a strong band at about 2000 Å may occur. It would, however, be unwise to carry this discussion further until more detailed information is available about the U.V. spectrum.

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THE CONSTITUTION OF THE DITERPENES, PHYLLOCLADENE, MIRENE, KAURENE, CRYPTOMERENE AND CUPRESSENE

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(Received 4 May 1959; in revised form 26 May 1959)

THE earlier literature on the diterpenes has been adequately reviewed.[1]

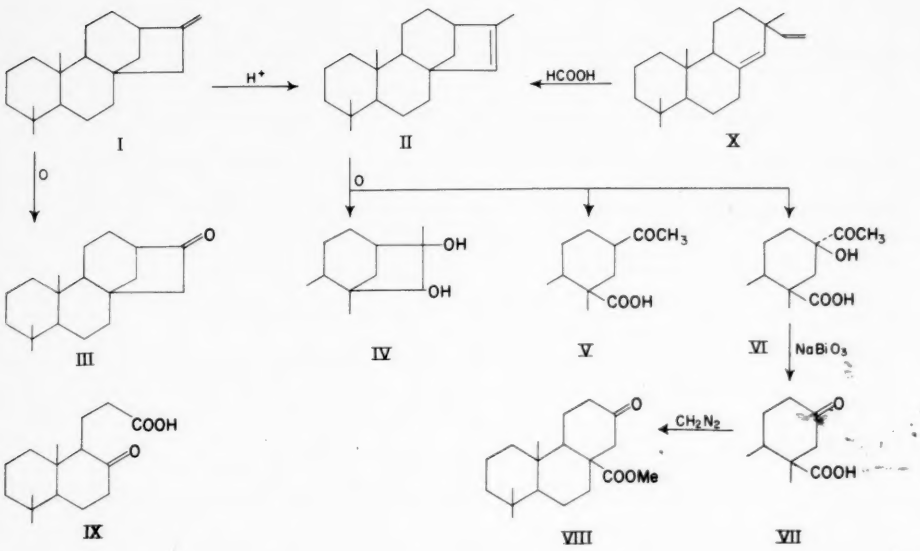
Phyllocladene.

Continuing the earlier work of Brandt,[2] stepwise degradation of phyllocladene has confirmed the structure of rings C and D of his proposed formula (I) for this diterpene,[3] although up till now, no direct chemical proof has been given for the constitution of rings A and B, including the position of the angular methyl group (see, however, the following papers). Many new compounds have been obtained but those having a bearing on the configuration are included in the following flow-sheet:

[1a] J. L. Simonsen and D. H. R. Barton, The Terpenes Vol. III, p. 334. Cambridge University Press (1952); [b] D. H. R. Barton, Quart. Rev. 3, 36 (1949).

[2] C. W. Brandt, New Zealand J. Sci. Tech. 34 B, 46 (1952).

[3] Cf. also W. Bottomley, A. R. H. Cole and D. E. White, J. Chem. Soc. 2624 (1955).



The properties of the previously prepared compounds (III), (IV), (V) and (VII)[2] have been confirmed. The compound, m.p. 215°, however, considered by Brandt[2] to have the constitution (IX), has the structure (VI) since it forms a λ-lactone, m.p. 175-176° (Found: C, 75.15; H, 9.9. $C_{20}H_{30}O_3$ requires C, 75.4; H, 9.5; infra-red bands at 1761 and 1706 cm^{-1}) and is oxidized by sodium bismuthate to the ketoacid (VII), identified by mixed m.p. and identical infra-red spectra. Esterification of (VII) with diazomethane yields the ketoester (VIII), m.p. 153-155.5 (Found: C, 74.8; H, 9.8. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.9).

The infra-red spectrum of the ketoester (VIII) indicates a carbonyl group in a six-membered ring (strong band at 1721 cm^{-1})[4] while its behaviour

to hydrolysis supports a sterically-hindered carboxyl group.

Kaurene.

The reactions of this diterpene agree with its formulation as a stereoisomer of phyllocladene (I). Chemically it behaves in an almost identical manner. Selenium dehydrogenation yields both retene and pimanthrene. Hydrogenation affords isomeric α[1]- and β-dihydrokaurene, m.p. 51-52° (Found: C, 87.6; H, 12.5. $C_{20}H_{34}$ requires C, 87.5; H, 12.5) while ozonization gives formaldehyde and a norketone, m.p. 113-115° [Found: C, 82.4; H, 10.5. $C_{19}H_{30}O$ requires C, 83.15; H, 11.0; 2:4-dinitrophenylhydrazone, m.p. 243-244° (Found: C, 66.0; H, 7.5; N, 12.5. $C_{25}H_{34}O_4N_4$ requires C, 66.05; H, 7.5; N, 12.3)] both reactions consistent with the grouping, $\overset{C}{C}\!<\!C = CH_2$, supported by the infra-red spectrum (strong band at 876 cm^{-1}), while the spectrum of the norketone shows that the carbonyl group is in a five-membered ring (strong band at 1745 cm^{-1})[4]. Kaurene may be isomerized with acids to isokaurene, containing the group, $\overset{C}{C}\!<\!C = C\!<\!\overset{H}{C}$ (band at 820 cm^{-1}), which on hydrogenation yields α-dihydrokaurene. This is analogous to the exocyclic - endocyclic double bond shift in the isomerization of phyllocladene into isophyllocladene (II).

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[4] L. H. Bellamy, The Infra-red Spectra of Complex Molecules (2nd Ed.), p. 132. Methuen, London (1958).

[5] K. Nishida and H. Uota, J. Agric. Chem. Soc. Japan 7, 157 (1931).

1959

Cryptomerene.

This has been shown (mixed melting point and infra-red spectrum) to be identical with isokaurene. The so-called λ-kaurene of Nishida and Uota[5] formed by the action of alcoholic sulphuric acid on kaurene or alcoholic potash on kaurene hydrochloride is, however, the corresponding alcohol, (Found: C, 82.7; H, 11.3. $C_{20}H_{34}O$ requires C, 82.7; H, 11.8) which with dry hydrogen chloride forms kaurene hydrochloride.

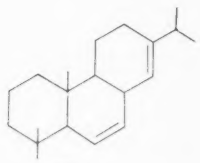
Mirene.

The infra-red spectrum of this diterpene is almost identical with that of phyllocladene and only varies at some points in the intensity of the bands. This evidence agrees with its being stereoisomeric with phyllocladene (I). As already recorded, it forms a monohydrochloride and a dihydro derivative different from α- and β-dihydrophyllocladene and α- and β-dihydrokaurene. Consistent with its having the group, $\begin{matrix}C\\C\end{matrix}\!\!>\!C = CH_2$, it forms a norketone, m.p. 98-99° (Found: C, 83.3; H, 10.5. $C_{19}H_{30}O$ requires C, 83.15; H, 11.0), similar to (III) by oxidation. Isomerization by heating with glacial acetic acid yields isophyllocladene.

Cupressene.

Owing to the small amount of this compound available no further constitutional work has yet been carried out. The infra-red spectrum exhibits strong bands at 823 and 743 cm^{-1}, consistent with the groups, $\begin{matrix}C\\C\end{matrix}\!\!>\!C = C\!<\!\begin{matrix}H\\C\end{matrix}$ and $\begin{matrix}H\\C\end{matrix}\!\!>\!C = C\!<\!\begin{matrix}H\\C\end{matrix}$. The ultra-violet spectrum indicates the absence of conjugation. Both bands are absent in the tetrahydroderivative which shows

no absorption in the 220 mμ region, indicating its saturated character.[6] As previously reported, attempted dehydrogenation with palladium-charcoal isomerized it to isophyllocladene, but it was stable to alcoholic sulphuric acid. A check on the infra-red spectrum of the material used showed the absence of any appreciable amount of isophyllocladene. On these and biogenetic grounds cupressene has been assigned the provisional formula (XI), although there are a number of alternative structures.



XI

Rimuene.

The evidence for its structure as (X) has recently been summarized.[7]

Assistance in this work is acknowledged in the following paper.

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[6] P. Bladon, H. B. Henbest and G. W. Wood, J. Chem. Soc. 2737 (1952).

[7] L. H. Briggs, B. F. Cain and J. K. Wilmshurst, Chem. & Ind. 599 (1958).

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THE ABSOLUTE CONFIGURATION OF PHYLLOCLADENE, MIRENE, RIMUENE, CUPRESSENE AND KAURENE

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1959

THE previous paper* summarizes the evidence for the constitution of the main naturally occurring diterpenes, this deals with their absolute configuration.

We agree with Ruzicka[1] and Wenkert[2,3] that biogenetically the diterpenes may be derived through a pimaradiene skeleton. Rimuene is stable to prolonged heating with glacial acetic acid, sulphuric acid (6%) in acetic acid, and 85% phosphoric acid and hence must have a stable configuration, particularly at C-13. Specifically, however, with formic acid it is converted into isophyllocladene, readily explained by the sequence, (I) - (IV). The intermediate carbonium ion (III) can yield either phyllocladene or isophyllocladene in biosyntheses (these two diterpenes co-occur in Araucaria excelsa and Phyllocladus trichomanoides)

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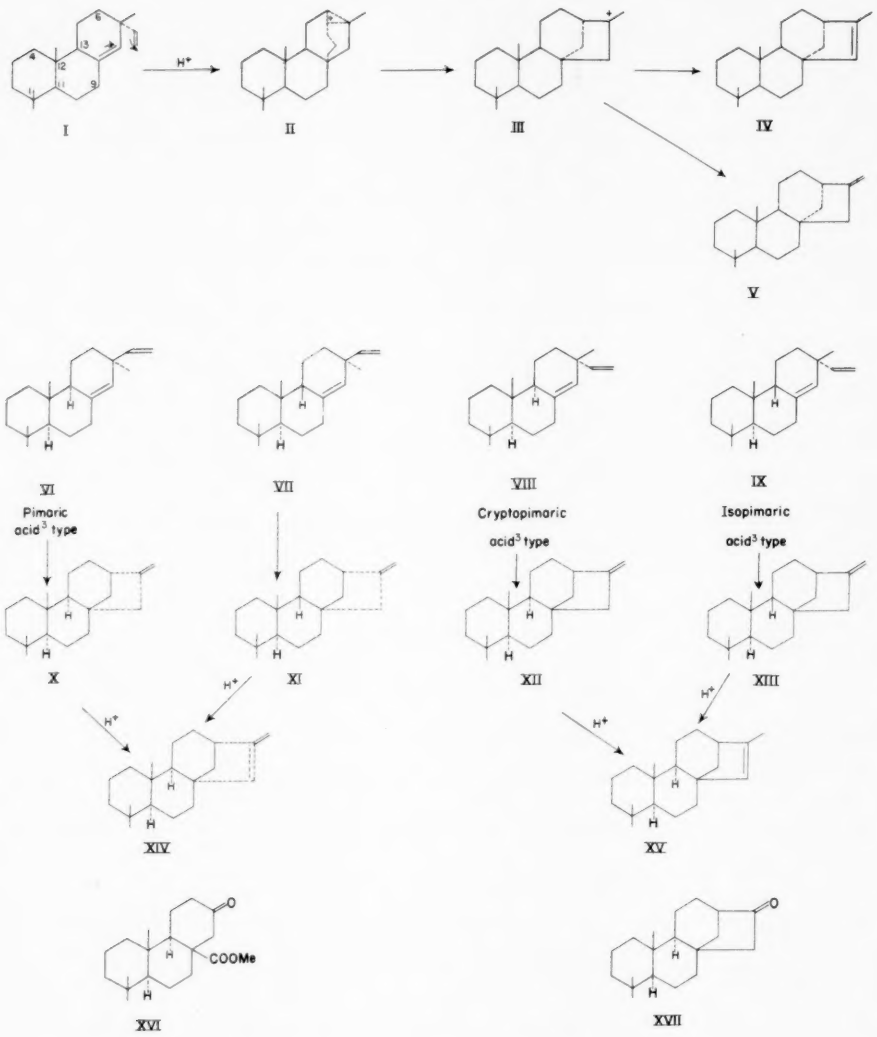
* L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, Tetrahedron Letters No. 8, 8 (1959).

1 L. Ruzicka, Experientia 9, 357 (1953).

2 E. Wenkert, Chem. & Ind. 282 (1955).

3 E. Wenkert and J. W. Chamberlin, J. Amer. Chem. Soc. 81, 688 (1959). This paper also summarizes the present position of the stereochemistry of the pimaric acids.



but only the more stable isophyllocladene by the above treatment. It should also be noted that the new bridged ring appears on the side opposite the original vinyl group which must take up a quasi-axial conformation in the first step.

This mechanism was first proposed by one of us[4] but a similar mechanism has also been suggested by Wenkert.[2]

The formation of the tetracyclic diterpenes can then be represented by (VI) - (XV).

It should be noted that in (XI) and (XIII) ring B must be in a boat form. In the further shift of the double bond from the exocyclic to the endocyclic position the less stable boat form can pass over to the more stable all-chair form of iso-hydrocarbon. Assuming that kaurene represents the more stable all-chair form then phyllocladene and kaurene must be (X) and (XII). The rotatory dispersion of the ketoester (XVI) derived from (XII) has a positive Cotton effect in agreement with that predicted by Djerassi[5] by the octant rule[6] while the ketoester from (X) has a predicted negative Cotton effect. Phyllocladene must therefore be (XII) and kaurene (X), and isophyllocladene and isokaurene (XV) and (XIV) respectively. Further, rimuene must be (VIII) (the more stable confirmation would have the vinyl group in quasi-equatorial position) and mirene (XIII).

Approximate calculations of the sign of the Cotton effect of the rotatory dispersions of the norketones from phyllocladene (XVII), mirene and kaurene likewise are in agreement with the observed results, positive, negative and positive respectively.

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[4] J. K. Wilmshurst, Thesis, University of New Zealand (1953).

[5] C. Djerassi, M. Cais and L. A. Mitscher, forthcoming publication.

[6] W. Moffitt, A. Moscowitz, R. B. Woodward, C. Djerassi and W. Klyne, forthcoming publication. We are most grateful to Professor Djerassi for sending us their data prior to publication.

Since cupressene is stable to alcoholic sulphuric acid but may be isomerized to isophyllocladene by heating with palladium charcoal[7] it, too, will have the same configuration at C-11, C-12 and C-13 as phyllocladene.

Finally, in support of this biogenetic scheme is the fact that ferruginol, sugiol (identified with isomiropinic acid by infra-red spectrum) and isopimaric (miropinic)[8] acid, all with proved normal trans A/B ring junctions, phyllocladene, mirene and kaurene all co-occur in Podocarpus ferrugineus.

We gratefully acknowledge assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science and the Research Grants Committee of the University of New Zealand and two of us (B.F.C. and B.R.D.) the award of Research Fund Fellowships. We are especially grateful to Professor Djerassi for measuring the optical rotatory dispersions discussed in this paper.

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[7] L. H. Briggs and M. D. Sutherland, J. Org. Chem. 7, 397 (1942).

[8] A. Brossi and O. Jeger, Helv. Chim. Acta 33, 722 (1950).

Tetrahedron Letters No. 8, pp. 17-19, 1959. Pergamon Press Ltd. Printed in Great Britain.

CONFIRMATION OF THE STRUCTURE OF PHYLLOCLADENE, MIRENE AND RIMUENE AND THE CONFIGURATION OF CUPRESSENE

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(Received 2 June 1959)

IN a previous paper[1] evidence for the constitution of the main naturally occurring crystalline diterpenes was summarized, while in a later paper[2] evidence was adduced for their absolute configuration. No direct chemical proof was given for the constitution of rings A and B nor for the position of the angular group which, on biogenetic grounds, was placed on C-12 although its position on C-11 could not theoretically be excluded.

These doubtful points in the constitution of rimuene, phyllocladene, mirene and cupressene have now been resolved and their absolute configuration confirmed by the conversion of rimuene into abieta-7:9(14)-diene of known constitution and absolute configuration.[3]

Earlier,[2] a mechanism, involving a Wagner - Meerwein transformation, was proposed for the conversion of rimuene into isophyllocladene. Ruzicka,

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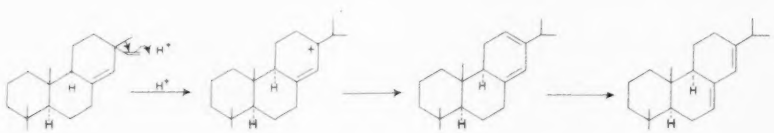
[1] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, Tetrahedron Letters No. 8, p. 8 (1959).

[2] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, Tetrahedron Letters No. 8, 13 (1959).

[3] W. Klyne, J. Chem. Soc. 3072 (1953).

however, has suggested[4] an alternative biogenetic scheme for the conversion of pimaradiene types of diterpenes into those of the levopimaric and neoabietic acid type. This has recently been realised in the laboratory by Wenkert and Chamberlin[5] with the conversion of both pimaric and isopimaric acid into abietic acid and now in our laboratory.

When rimuene is heated with formic acid for 2-3 days the major product, besides isophyllocladene, is an isomeric liquid hydrocarbon, b.p. 125°/0.3 mm, $[\alpha]_D^{25}$ - 196°, λ_{max}^{EtOH} 272.5 mμ (log ε 3.21) but with further reflux periods (5-10 days) the major product is another isomeric liquid hydrocarbon which, after distillation from sodium, had b.p. 138°/0.2 mm, $[\alpha]_D^{21}$ - 80.3° ± 3°, n_D^{22} 1.5320, λ_{max}^{EtOH} 239 mμ (log ε 4.30). The maxima correspond to diene systems of the levopimaric and abietic acid type respectively (λ_{max} 272.5 and 241 mμ) and the isomerization may be formulated (I) - (IV).



I II III IV

Obviously (III) is an intermediate in the reaction, isomerizing to the

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[4] L. Ruzicka, Experientia 9, 357 (1953).

[5] E. Wenkert and J. W. Chamberlin, J. Amer. Chem. Soc. 81, 688 (1959).

[6] L. Ruzicka, H. Waldmann, P. J. Meier and H. Hösli, Helv. Chim. Acta 16, 169 (1933).

more stable abietadiene type on longer treatment.

Abieta-7:9(14)-diene has been prepared from abietic acid by a modification of Ruzicka et al.,[6] Reduction with lithium aluminium hydride afforded abieta-7:9(14)-dien-15-ol,[6] oxidized by t-butyl chromate[7] to the corresponding aldehyde.[6] Reduction of the derived semicarbazone by the Wolff - Kishner method gave abieta-7:9(14)-diene with properties similar to those recorded.[6] Our product, after distillation from sodium, had b.p. 133° (bath temp.)/0.1 mm, $[\alpha]_D^{21}$ - 86°, λ_{max}^{EtOH} 241 mμ (log ϵ 4.29) while Ruzicka et al.[6] record b.p. 135-138°/0.15 mm, n_D^{24} 1.5313. These properties indicate the identity of the dienes from both rimuene and abietic acid, confirmed by identical infra-red spectra.

Since the constitution and absolute configuration of abietic acid is known[3] and since rimuene, phyllocladene, mirene and cupressene can be isomerized to a common isomer, isophyllocladene, the constitutions and absolute configurations of rimuene, phyllocladene, mirene and the partial structure of cupressene, set out in the earlier papers[1,2] are confirmed while this evidence and biogenetic considerations support the constitution and absolute configuration proposed for kaurene.[2]

We gratefully acknowledge assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science and the Research Grants Committee of the University of New Zealand.

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[7] R. V. Oppenauer and H. Oberrauch, Anal. Assoc. Quim. Arg. 37, 246 (1949).

Tetrahedron Letters No. 8, pp.20-24, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF THELEPHORIC ACID

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Department of Chemistry, University of Delhi

(Received 8 June 1959)

IN the course of our investigation of Indian lichens, a species of Lobaria obtained from Darjeeling yielded a dark purple and sparingly soluble compound agreeing closely with the description[1,2] of thelephoric acid in properties, colour reactions, its elemental composition and that of its derivatives. It did not melt below 360° and had the composition of $C_{20}H_{12}O_9$. The triacetate ($C_{26}H_{18}O_{12}$) crystallized from nitrobenzene as orange-red needles, m.p. 330° (decomp.). The leuco penta-acetate ($C_{30}H_{24}O_{14}$), obtained as colourless needles from nitrobenzene, did not melt below 360°. Through the kindness of Prof. S. Shibata, a sample of thelephoric acid[2] which had been isolated from the lichen Lobaria retigera and which had also been compared with thelephoric acid isolated from the fungus Thelephora palmata, was made available for comparison and there was full agreement

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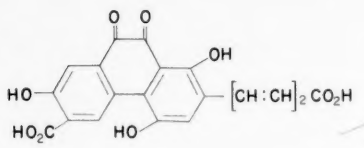
[1] F. Kögl, H. Erxleben and L. Jänecki, Ann. 482, 110 (1930).

[2] Y. Asahina and S. Shibata, Ber. 72, 1531 (1939).

between this sample and ours. Comparison was effected using infra-red and ultra-violet spectra and X-ray diffraction pattern also.



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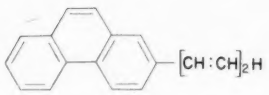

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Kögl et al.[1] made a detailed investigation of the structure of thelephoric acid and formulated it as a derivative of phenanthrenequinone (I). By the zinc dust distillation of its triacetate they obtained a hydrocarbon $C_{18}H_{14}$ (m.p. 125°), for which they assigned the structure 1-2'-phenanthrylbuta-1:3-diene (II). Millward and Whiting[3] recently synthesized trans-1-2'-phenanthrylbuta-1:3-diene and found it to have a different melting point (107-109°). Since the original sample of Kogl was not available for comparison, the question of identity could not be settled. We have, therefore, carried out the zinc dust distillation of the triacetate of thelephoric acid. Our product was different from the one reported by Kögl et al.[1] It had m.p. 202-205° and its ultra-violet spectrum had a single maximum at 2795 Å ($E^{1\%}_{1cm}$ 1253 in $CHCl_3$); it was identified as terphenyl. A synthetic sample, prepared for comparison,[4]

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[3] B. B. Millward and M. C. Whiting, J. Chem. Soc. 903 (1958).

[4] H. France, I. M. Heilbron and D. H. Hey, J. Chem. Soc. 1370 (1938).

exhibited a single maximum in the ultra-violet region[5] at 2790 Å ($E^{1\%}_{1cm}$ 1258 in $CHCl_3$), melted at 207-209° and the mixed m.p. with the zinc dust distillation product was 205-207°. As terphenyl (m.p. 202-205°) had been obtained by the zinc dust distillation of polyporic acid,[6] muscarufin[7] and other terphenylquinones,[8] it seemed quite likely that thelephoric acid also is a derivative of terphenylquinone.

In order to test for the butadiene side chain which had been postulated to be present in thelephoric acid,[1] the leuco penta-acetate was subjected to condensation with maleic anhydride by refluxing the reactants for 3 hr in nitrobenzene medium (compare leuco acetate of muscarufin[7]). The Diels-Alder reaction did not take place.

Catalytic reduction of thelephoric acid followed by permethylation with excess of diazomethane yielded two products as reported by Kögl et al., one sparingly soluble, m.p. 254-256° (earlier reported m.p. 246°) and another more soluble in alcohol. The first fraction was obtained after a number of crystallizations from chloroform and ether, and its analysis agreed with the requirements of a heptamethyl ether. Thus while thelephoric acid formed only a leuco penta-acetate, it yielded a hepta-methyl ether after reduction and permethylation. Kögl et al.[1] explained

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5 A. E. Gillam and D. H. Hey, J. Chem. Soc. 1171 (1939).

6 F. Kögl, Ann. 447, 78 (1926); J. Murray, J. Chem. Soc. 1345 (1952).

7 F. Kögl and H. Erxleben, Ann. 479, 11 (1930).

8 M. Akagi, J. Pharm. Soc. Japan 62, 129 (1942).

this by assuming the presence of two carboxyl groups in thelephoric acid. When we examined the infra-red spectrum of the heptamethyl ether we found no absorption which could be attributed to ester groupings. It had only one strong band in the double bond and carbonyl region at 6.12 μ and this could not be attributed to any ester group. This conclusion was further confirmed by the fact that the heptamethyl ether did not undergo any reduction with lithium aluminium hydride in dioxane solution.

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The above findings necessitate a revision of the formula for thelephoric acid. Of the twenty carbon atoms in the molecule, eighteen are accounted for by the terphenyl system, and of the nine oxygen atoms, two can be placed in the benzoquinone system and three in the three hydroxyl groups. Then two carbon atoms and four oxygen atoms are left. Since there are no carboxyl groups, a possibility that suggests itself is the presence of two methylenedioxy groups in the molecule. The test performed according to the method of Feigl[9] showed them to be present in thelephoric acid and its derivatives. The heptamethyl ether gave positive evidence for the presence of methylenedioxy group when the test was carried out following the modified method of Schmid et al.[10]

Oxidation of thelephoric acid with alkaline hydrogen peroxide was next attempted employing Kögl's procedure.[1] We could obtain only a trace of acidic products which showed positive tests for the methylenedioxy groups

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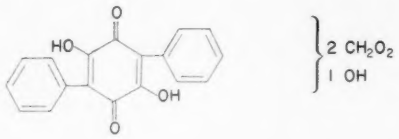
[9] F. Feigl, Spot Tests in Organic Analysis p. 190. Elsevier, Amsterdam (1956).

[10] J. Eisenbeiss and H. Schmid, Helv. Chim. Acta 42, 61 (1959).

according to the method of Schmid et al.,[10] but we have not so far been able to isolate any crystalline substance in this reaction. Due to shortage of material, we could not pursue this observation further immediately and hope to do so shortly. The results so far obtained indicate that thelephoric acid is a derivative of polyporic acid having the partial structure (III).



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The increase in methoxyl groups after reduction and permethylation may be due to the reason that one of the methylenedioxy groups might have undergone cleavage under the reducing conditions. Although such a reaction does not appear to have been reported before, the above mentioned observation suggests this possibility.

We convey our thanks to Mr. M. V. R. Rao of our department for the X-ray analysis, and to Professor S. Shibata of Tokyo for the sample of thelephoric acid.

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RING-ISOMERIC CHANGE IN ISOFLAVONES:

SYNTHESIS OF 5,7-DIMETHOXY-6-HYDROXYISOFLAVONE, MUNINGIN AND 5,7-DIHYDROXY-6-METHOXYISOFLAVONE

M. L. DHAR and T. R. SESHADRI
Department of Chemistry, University of Delhi

Abstract—The above mentioned compounds have been prepared by methods involving isomeric change from the more readily available 5,7,8-substituted isoflavones.

SYNTHESIS OF SOME ISOQUINOLINE DERIVATIVES

RYUGI TACHIKAWA
Faculty of Pharmaceutical Sciences, University of Tokyo

Abstract—The Bischler–Napieralski reaction has been applied to the synthesis of several isoquinoline derivatives related to papaverine but devoid of one or two methoxyl groups in positions 6 and 7.

STUDIES ON THE STEROIDAL COMPONENTS OF DOMESTIC PLANTS—XIX

THE STRUCTURE OF KOGAGENIN, A SAPOGENIN FROM *DIOSCOREA TOKORO*, MAKINO[2]

KEN'ICHI TAKEDA, TOKUO KUBOTA and (in part) ARIMASA SHIMAOKA
Research Laboratory, Shionogi & Co. Ltd. Osaka, Japan

Abstract—The structure of kogagenin, a steroidal sapogenin isolated from the epigeous part of *Dioscorea tokoro*, Makino, has been shown to be 25D-spirostane-1β,2β,3α,5β-tetrol. This sapogenin is the first example of a naturally occurring spirostane tetrol.

STEREOCHEMICAL IMPLICATIONS IN SESQUITERPENE BIOGENESIS

J. B. HENDRICKSON
University of California, Los Angeles, California

Abstract—The biogenesis of the sesquiterpenes is envisioned as a displacement of the allylic hydroxyl of farnesol by either of the isolated double bonds, giving rise to versatile 6-, 10-, or 11-membered ring intermediates. The medium-ring intermediates possess unique conformations which dictate the structure as well as stereochemistry of the sesquiterpenes derived from them by a variety of simple further reactions, notably double-bond cyclizations.

ISOLATION AND STRUCTURE OF THE FLUORESCENT SUBSTANCES FORMED IN THE OXIDATIVE REACTION OF ADRENALINE AND NORADRENALINE WITH ETHYLENEDIAMINE

J. HARLEY-MASON and A. H. LAIRD
University Chemical Laboratory, Cambridge

Abstract—One of the fluorescent products formed in the oxidative reaction of adrenaline with ethylenediamine has been characterised as 2,3-dihydro-3-hydroxy-l-methylpyrrolo-4,5-g quinoxaline (III). In the case of noradrenaline, the only fluorescent product found has been characterised as 1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene (VII). The same tetrahydrotetra-aza-anthracene is also obtained from catechol, 2-methylnoradrenaline, adrenalone and 3,4-dihydroxymandelic acid. The chemistry and mechanism of formation of III and VII are discussed.

STRUCTURE MOLECULAIRE ET ACTIVITE OESTROGENE—XVII*

COMPARAISON DES CONFIGURATIONS ABSOLUES DES ACIDES BISDEHYDRODOISYNOLIQUE NORMAL ET α, α-DIMETHYL β-ETHYL ALLENOLIQUE PHYSIOLOGIQUEMENT ACTIFS

R. GAY et A. HOREAU
Laboratoire de Chimie Organique des Hormones, Collège de France, Place Marcelin Berthelot, Paris (Ve) et Faculté des Sciences de Dijon, Bld. Gabriel Dijon (Côte d'Or)

Résume—Les configurations des acides fortement oestrogènes: acide α,α-diméthyl β-éthyl allénolique *gauche* et acide *n*-bisdéhydrodoisynolique *gauche* ont été déterminées comparativement.

Abstract—A stereochemical correlation has been established between the two highly estrogenic acids: levorotatory α,α-diméthyl β-éthyl allenolic acid (I) and levorotatory *n*-bisdehydrodoisynolic acid (III). The configuration of the corresponding asymetric centre is *opposite* in these compounds.

1959

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Tetrahedron Letters No. 9, pp. 1-4, 1959. Pergamon Press Ltd. Printed in Great Britain.

CONSTITUTION OF VICANICIN FROM THE LICHEN TELOSCHISTES FLAVICANS

S. Neelakantan, T. R. Seshadri and S. S. Subramanian*

Department of Chemistry, University of Delhi

(Received 8 June 1959)

TELOSCHISTES FLAVICANS has been found to contain besides anthraquinone pigments, a colourless substance. The former have been found to vary in composition,[1-3] but the colourless substance seems to have been the same in all the samples of the lichen and by employing column chromatography (magnesium carbonate) nearly 1% yield on the dry weight of the lichen could be secured. It has now been given the name "vicanicin" based on the species name of the lichen, omitting the first syllable in view of the compound being colourless.

Vicanicin crystallized from benzene as colourless stout needles, m.p. 248-250°. It had the molecular formula $C_{17}H_{14}O_5Cl_2$** with one methoxyl

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* Dept. of Pharmacy, Andhra University, Waltair.

** Satisfactory analyses were obtained for all the compounds described here.

1 W. Zopf, Ann. 340, 300 (1905).

2 T. R. Seshadri and S. S. Subramanian, Proc. Indian Acad. Sci. 30A, 67 (1949).

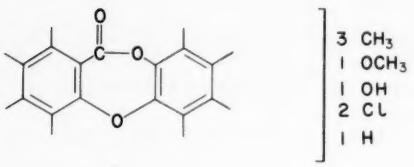
3 T. R. Rajagopalan and T. R. Seshadri, Proc. Indian Acad. Sci. 49A, 1 (1959).

and three C-methyl groups. The crystalline solid did not readily dissolve in aqueous sodium hydroxide but a fine suspension of it, obtained by the dilution of an ethanolic solution with water, dissolved easily in the alkali and the solution turned pink on long standing. It did not give any prominent colour with either alcoholic ferric chloride or concentrated sulphuric acid.

The presence of a free hydroxyl group was shown by the ready formation of a monoacetate ($C_{19}H_{16}O_6Cl_2$), m.p. 213-214°, and of a monobenzoate ($C_{24}H_{18}O_6Cl_2$), m.p. 190-191°. This hydroxyl was phenolic in nature since it underwent easy methylation and ethylation with the appropriate alkyl iodide and potassium carbonate: monomethyl ether ($C_{18}H_{16}O_5Cl_2$), m.p. 193-194°; monoethyl ether ($C_{19}H_{18}O_5Cl_2$), m.p. 185-186°.

Vicanicin gave evidence for the presence of a lactone ring. By the action of aqueous 2 N-sodium hydroxide in dioxane solution, O-methylvicanicin formed a hydroxy acid (O-methylvicanicic acid, $C_{18}H_{18}O_6Cl_2$), m.p. 217-218°. On the other hand when refluxed with absolute methanolic sodium methoxide, a methyl ester (methyl O-methylvicanicate, $C_{19}H_{20}O_6Cl_2$), m.p. 155-156°, was formed. When this was further methylated, it gave rise to a neutral product ($C_{20}H_{22}O_6Cl_2$), m.p. 97-98, agreeing with the requirements of an ether-ester derived from the lactone.

Of the five oxygen atoms, four had been accounted for as one in the methoxyl, one in the hydroxyl and two in the lactone. The fifth oxygen was inert and could be placed in a diphenyl ether linkage. All these considerations suggested the possibility of vicanicin being a chloro-depsidone of the partial formula (I).



I

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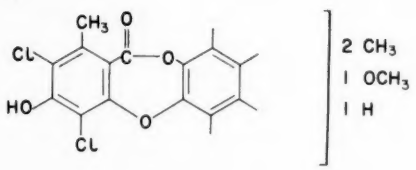
This was supported by spectral studies. In ultra-violet light, vicanicin had maximum absorption at 270 mμ and an inflexion at 324 mμ. For comparison, the ultra-violet spectrum of diploicin was taken and it had the maximum absorption at 270 mμ and an inflexion at 321 mμ. Robertson and co-workers[4] reported that nidulin had a maximum absorption at 267 mμ and an inflexion at 323 mμ and for nornidulin, the corresponding values were 266 mμ and 323 mμ. The infra-red spectra of vicanicin and diploicin were very similar. These data led to the development of the formula (II) indicating the common structure of the left half in all the four compounds, diploicin, nidulin, nornidulin and vicanicin.



II

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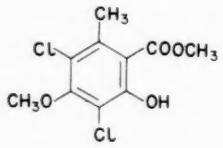
[4] F. M. Dean, J. C. Roberts and A. Robertson, J. Chem. Soc. 1432 (1954).

Two methods had been used in the past for splitting molecules of this type: (i) perchlorination of the methyl ester of the corresponding hydroxy acid followed by reduction and methanolysis;[5] (ii) oxidation of the ester with concentrated nitric acid and glacial acetic acid.[4] Using the second method and methyl O-methylvicanicate, methyl 3:5-dichloroeverninate (III), m.p. 78°, could be obtained as one product; this confirmed structure (II). In this oxidation, a small quantity of an orange-red quinone could be isolated from the sodium bicarbonate-soluble fraction. It gave a characteristic purple colour in alkaline solution (λ_{max} 532 mμ in buffer solution, pH 10.4) and was almost certainly 2-hydroxy-3:6-dimethyl-p-benzoquinone (IV) which was reported to have λ_{max} 530 mμ (in buffer solution, pH 10.4). On the basis of this result, the structure of vicanicin could be completed as in (V) which would also be in comformity with its possible formation from an orsellinic unit and a C-methylorsellinic unit.



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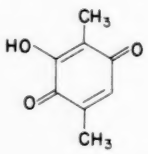

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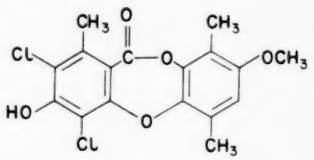

V

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[5] T. J. Nolan, J. Algar, E. P. McCann, W. A. Manahan and N. Nolan, Sci. Proc. R. Dublin Soc. 24, 319 (1948).

[6] L. F. Fieser and M. I. Ardao, J. Amer. Chem. Soc. 78, 776 (1956).

Tetrahedron Letters No. 9 pp. 5-9, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE SPECIFICITY OF THE OZONIZATION OF POLYCYCLIC AROMATICS

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(Received 12 June 1959)

1959

THE reaction of ozone with polycyclic aromatics has received much attention in recent years.[1-6] Moriconi et al.,[1-4] Copeland et al.[5] and Bailey et al.[6] thus have studied the ozonolysis of naphthalene,[6] anthracene,[5,6] naphthacene,[3,5] phenanthrene,[1,5,6] chrysene,[5] benz(a)-anthracene,[2,5] dibenz(a,h)anthracene,[4] triphenylene,[5] perylene,[5] pyrene,[6] and acenaphthylene.[5] Ozone was found to react in most cases by 1,2-addition to aromatic bonds to give ultimately aldehydes and acids presumably via Criegee's[7] Zwitterion. In several instances however ozone also reacted by 1,4-addition to para-positions[2,6] possibly via Bailey's[6] mechanism. The major products isolated can be accounted for by postulating a 1,2- or a simultaneous 1,2- and 1,4-addition of ozone to polycyclic

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1 W. F. O'Connor, W. J. Schmitt and E. J. Moriconi, Industr. Engng. Chem. 49, 1701 (1957); J. Amer. Chem. Soc. 77, 5640 (1955).

2 E. J. Moriconi, W. F. O'Connor and F. T. Wallenberger, Chem. & Ind. 22 (1959); J. Amer. Chem. Soc. In press.

3 E. J. Moriconi, W. F. O'Connor and L. Taranko, Arch. Biochem. Biophys. In press. (Private Communication).

4 E. J. Moriconi, G. W. Cogswell, W. J. Schmitt and W. F. O'Connor, Chem. & Ind. 1591 (1958).

5 P. G. Copeland, R. E. Dean and D. McNeil, Chem. & Ind. 329 (1959).

6 P. S. Bailey, Chem. Rev. 58, 965 (1958).

7 R. Criegee and G. Lohaus, Ann. 583, 6 (1953).

aromatics.[2] Formation of polymeric by-products, presumably derived from partial destructive ozonization quite frequently precludes complete or quantitative assessment of all reaction products.[2,5,6]

Recently a theoretical correlation has been suggested[2] which offered for the first time a consistent explanation why ozone reacts by 1,2-addition with some aromatics and by 1,4-addition with others. Assuming that the preferred course of the reaction depends predominantly upon the relative stability of various ortho and para dihydro structures characteristic of transitional or intermediate ozone adducts, it has been shown that quinone-hydroquinone redox potentials[8] can be used as measure of such stabilities[9] in the correlation with the preferred course of ozonolysis. Unfortunately only few redox potentials have been determined experimentally.

A new and more universally applicable relationship has now been established in form of calculated resonance energy decreases which accompany the reaction. Such resonance energies are available in the literature for ortho positions[10] and were calculated for para positions from para localization energies[11] according to a suggestion of Wheland.[12] A correlation of resonance energies (R.E.) and redox potentials (E_o) with the preferred course of ozonization (Table 1) shows that ozone indeed reacts preferentially with positions which lead to the more stable transitional or

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[8] L. F. Fieser in H. Gilman's Organic Chemistry Vol I (2nd Ed.), p. 159. John Wiley, New York (1945).

[9] G. E. K. Branch and M. Calvin, The Theory of Organic Chemistry p. 303. Prentice Hall, New York (1944).

[10] R. D. Brown, J. Chem. Soc. 3249 (1950).

[11] R. D. Brown, J. Chem. Soc. 691 (1950); 1612 (1951).

[12] G. W. Wheland, Resonance in Organic Chemistry pp. 379-381. John Wiley, New York (1955).

TABLE 1. Preferred 1,2- and 1,4- addition of ozone

Hydrocarbon in C. A. nomenclature	Positions in C. A. numbering	Resonance energy (kcal)	Redox[2,8] potential (V)	Preferred ozonization (Positions)	Reference
Naphthalene	1,2-	20.0	0.501	1,2-	6
	1,4-	27.6	0.534		
Anthracene	1,2-	20.0	0.415	9,10 1,2-	5,6
	1,4-	25.6	0.451		
	9,10-	15.6	0.254		
Naphthacene	1,2-	19.5	—	5,12-	3,5
	1,4-	24.6	—		
	5,12-	13.6	-0.315		
Phenanthrene	1,2-	23.9	0.586	9,10-	1,5,6
	3,4-	24.4	0.571		
	1,4-	29.6	0.598		
	9,10-	16.0	0.410		
Chrysene	1,2-	23.6	—	5,6-	5
	3,4-	23.3	—		
	5,6-	18.1	0.440		
	1,4-	28.6	—		
Benz(a)anthracene	5,6-	15.3	0.380	7,12--5,6	2,5
	7,12-	19.6	0.353		
Dibenz(a, h)anthracene	5,6-	15.7	—	5,6-	4
	7,14-	22.6	0.418		
Triphenylene	1,2-	25.8	—	1,2-	5
	2,3-	32.1	—		
	1,4-	30.0	—		
Pyrene	4,5-	16.0	0.420	4,5	6

intermediate 1,2- or 1,4-adduct, since the lower the R.E.[10] and the E_o,[9] the more stable the corresponding ortho or para dihydro structure.

Most compounds listed in Table 1 except anthracene, benz(a)anthracene and naphthacene react predominantly by 1,2-additions. This is in agreement with theoretical predictions: $R.E._{ortho} < R.E._{para}$ and $E_{o_{ortho}} < E_{o_{para}}$.

Naphthacene[3,5] and anthracene[5,6] give predominantly the corresponding quinones via 1,4-addition of ozone. This likewise is in agreement with the proposed correlations: $R.E._{ortho} > R.E._{para}$ and $E_{o_{ortho}} > E_{o_{para}}$. Small amounts of 2,3-naphthalenedicarboxylic acid were obtained recently from the ozonization of anthracene in addition to large amounts of anthraquinone.[5] The competing 1,2-addition of ozone to the 1,2- and 3,4-bonds of anthracene is accordingly much slower (less preferred) than the 1,4-addition.

Benz(a)anthracene is also capable of both types of reaction. Ozonolysis under different conditions[2,5] gave by 1,4-addition the isolable intermediate benz(a)anthraquinone[2,5] and its further ozonization product 1,2-anthraquinone-dicarboxylic acid[2] and by 1,2-addition,4,5-benzdiphenic acid.[5] Redox potentials tend to favor a predominantly 1,4-addition while resonance energies are in favor of a predominantly 1,2-addition. This singular exception among paralleling R. E. and E_o values in Table 1 might well imply that both reaction paths are nearly equivalent. This then is in agreement with the experimental results.

Thus resonance energies have been found to be a powerful tool to account for and to predict the most reactive sites (bonds or positions) of polycyclic aromatics towards ozone. Predictions can be extended[10,11,12] to compounds not listed in this communication. Furthermore, the discussed correlation

lends itself to establish an approximate order of decreasing ease of ozonolysis in the series of unsubstituted polycyclic aromatic hydrocarbons with triphenylene as least and naphthacene as most reactive.

1959

Tetrahedron Letters No. 9, pp. 10-12, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE SYNTHESIS OF 1-METHYL-2:3,6:7-DIBENZO-1,4, 5-TRIAZA-CYCLOHEPTA-2,6-DIENE[1]

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(Received 15 June 1959)

SINCE the application of the simple molecular orbital theory to aromatic compounds by Hückel[3] the method has been used extensively to calculate resonance energies of conjugated systems, and the energies so found have been in exceedingly good agreement with experimental values. The ability of the theory to yield accurate predictions of aromaticity has been dramatically demonstrated in the cases of the tropylium[4] and cyclopropenium[5] ions, but there appears to be only one authentic report[6] of a monocyclic conjugated system containing $(4n + 2)$ π-electrons for which $n > 1$. The resonance energy in this latter system has not yet been reported, and no experimental evidence for aromaticity was cited.

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[1] Supported in part by a research grant from the National Science Foundation.

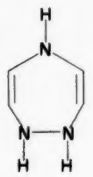
[2] National Science Foundation Predoctoral Fellow, 1956-1959.

[3] E. Hückel, Z. Physik 70, 204 (1931).

[4] W. von E. Doering and L. H. Knox, J. Amer. Chem. Soc. 76, 3203 (1954).

[5] R. Breslow and C. Yuan, J. Amer. Chem. Soc. 80, 5991 (1958).

[6] F. Sondheimer and R. Wolovsky, J. Amer. Chem. Soc. 81, 1771 (1959).



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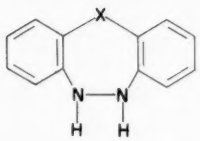

II

X=a, $-N-CH_3$
b, $-O-$
c, $-S-$
d, $-CH_2-$

1959

Structure I is a monocyclic system which contains ten π-electrons and is capable of planarity without undue strain. The resonance energy of the planar system, calculated with all the usual approximations[3,7] and taking the value[7] of the nitrogen Coulomb integral as 0.5β, is 2.47β. The dibenzo derivative (IIa) was similarly found to have a resonance energy of 6.34β, or 2.34β above that of the two benzene rings.[8]

Derivatives of I, which represents a heretofore completely unknown type of potentially aromatic system,[9] have now been synthesized. The compounds prepared were IIa, IIb, and IIc. As a model compound lacking the essential features required for a large resonance energy, IId was

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[7] C. A. Coulson, Valence p. 238. Oxford Press, London (1952).

[8] The molecular orbital calculations for I, II and related structures were carried out be matrix diagonalization utilizing an IBM 650 computer, and the details will be presented in the full publication.

[9] Compounds containing this ring system were reported by P. C. Guha and M. K. De, Quart. J. Indian Chem. Soc. 3, 41 (1926). The substances described by these authors were prepared by improbable reactions, were not properly characterized, and do not have the characteristic properties which have been found in the present work. It is exceedingly unlikely that any of them actually contain the 10 π-electron ring system in question. The earlier claim of a synthesis of IIc has been retracted H. H. Szmant and Y. L. Chow, J. Amer. Chem. Soc. 79, 5584 (1957) .

also prepared. The synthetic procedures used were similar in each case. N-methyl-2,2'-dinitro-diphenylamine was reduced to the cyclic azo compound (1-methyl-2:3,6:7-dibenzo-1,4,5-triaza-cyclohepta-2,4,6-triene) as red needles in 21% yield using lithium aluminum hydride in tetrahydrofuran (Found: C, 74.53; H, 5.59; N, 20.01). The azo compound absorbed two moles of hydrogen upon catalytic reduction, and yielded 2,2'-diamino-diphenylmethylamine (III) m.p. 88°. When the azo compound was reduced with Raney nickel and hydrazine,[10] IIa (1-methyl-2:3,6:7-dibenzo-1,4,5-triazacyclohepta-2,6-diene) was isolated in 91% yield, as a colorless crystalline solid, m.p. 93.5-95°. Found: C, 73.91; H, 6.18; N, 19.93, mol. wt. (Rast) 219. The compound absorbed one mole of hydrogen upon catalytic reduction and yielded the amine III. Upon oxidation with mercuric oxide, IIa was converted back to the azo compound. Compounds IIb, c, and d were prepared by analogous series of reactions. All of the hydrazo compounds[11] show bands in the infrared at 3.0 and 3.1μ. Compound IIa reacted irreversibly with dilute acid, (reminiscent of pyrrole) which prevented pK measurements.

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[10] S. Hornsby and W. L. Peacock, Chem. & Ind. 858 (1958).

[11] Crystallographic studies of these compounds by the X-ray method have been undertaken by Professor K. N. Trueblood, University of California at Los Angeles.

Tetrahedron Letters No. 9, pp. 13-17, 1959. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE, STEREOCHEMISTRY AND ABSOLUTE CONFIGURATION OF AGAROL, A NEW SESQUITERPENE ALCOHOL FROM AGARWOOD OIL

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(Received 19 June 1959)

1959

FROM the solvent-extracted essential oil of the fungus infected plant Aquilaria agallocha, Roxb.[1], the main characteristic constituent, an α,β-unsaturated monoethynoid eudalenic primary alcohol named agarol has been isolated in pure form by batch strip fractionation and column chromatography on alumina (grade II and IV). Its structure, stereochemistry and absolute configuration are reported in this communication.

Agarol [b.p. 117°/0.9 mm (inside temperature),[2] $[\alpha]_D^{23}$ -21.8° (C, 7.23), n_D^{29} 1.5052, d_4^{30} 0.9785; number of double bonds: 1 (Peracid - 1.06, catalytic hydrogenation - 1.02); M_D 67.81, Calc. for $C_{15}H_{25}OH$, 1 $\left|\begin{matrix}=\\:\end{matrix}\right.$67.79; no characteristic U.V. absorption, I.R. spectrum: 885 cm^{-1} ($>C = CH_2$), 3322 cm^{-1} (-OH); (Calc. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.6; H, 11.4)] forms a monoacetate (Pyr. $-Ac_2O$)

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[1] Sadgopal and B. S. Varma, Soap, Perf. & Cosmetics 25, 169 (1952).

[2] Unless specified to the contrary, b.p. refers to bath temperature, $[\alpha]_D$ are for $CHCl_3$ solution; all products except solid derivatives were chromatographed over alumina; ultra-violet absorption spectra were determined on EtOH solution.

[b.p. 132°/0.3 mm, $[\alpha]_D^{23}$ -10° (C, 1.4); I.R.Spectrum: 1723 cm^{-1} (acetoxy group), 885 cm^{-1} ($>C = CH_2$); (Calc. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.7; H, 10.9)] and gives a positive xanthate test (primary or secondary alcoholic group).

Primary α,β-unsaturated nature of the alcoholic group is revealed by its oxidation with CrO_3(HOAc) and MnO_2 ($CHCl_3$) to α,β-unsaturated aldehyde (Fehling's and Tollens' tests positive)- agaral (Calc. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 80.5; H, 11.2); λ_{max} 243 and 320 mμ (ε 8480 and 72 respectively).

Methylenic nature ($>C=CH_2$) of the only double bond in agarol was revealed by, the formation of copious amount of formaldehyde during ozonolysis (dimedone derivative, m.p. and mixed m.p.), positive chromotropic acid test, strong absorption band at 885 cm^{-1} (both in agarol and its acetate) and the disappearance of the same in dihydroagarol.

Dehydrogenation of agarol with Se and Pd-C furnished eudalene (characterized through its spectrum and picrate, m.p. and mixed m.p. 90°). (Calc. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63; N, 10.17. Found: C, 57.3; H, 4.68; N, 9.9) from which the partial expression (I) is arrived at for it.

The remaining carbon atom is presumably an angular methyl group (not geminal as shown by the absence of doublet in the region 1368 cm^{-1})[3], which assuming agarol obeys isoprene rule, can be located at C(10) in

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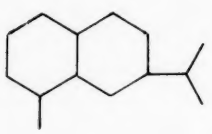
[3] A. R. H. Cole in Zechmeister's, Progress in the Chemistry of Organic Natural Products Vol. XIII, p. 44. Springer, Vienna (1956).

1959



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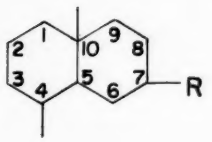
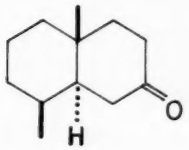


II, R = $-C(=CH_2)-CH_2OH$

III, R = $-C(=O)-CH_2OH$

IV, R = O



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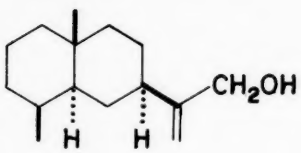
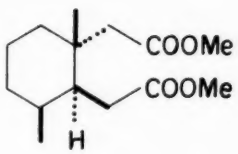


VII



VI

which case the basic formula for agarol should be (II), this premise being further supported by degradation experiments described in the sequel. Numbering of carbon atoms is in accordance with Barton's formulation.[4]

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[4] D. H. R. Barton, P. de Mayo and M. Shafiq, J. Chem. Soc. 929 (1957); O. Motl, V. Herout and F. Sorm, Coll. Czech. Chem. Comm. 23, 1293 (1958).

On ozonolysis agarol, apart from formaldehyde affords hydroxyacetone (iodoform test, Feigl's periodate test, green coloured acyloinoxime type copper complex[5] from its oxime, presumably formed through isopropylidene - isopropenyl transformation) and two other key compounds: Ketol (III) [b.p. 170°/0.5 mm, (Calc. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.53; H, 10.50); I.R. spectrum: 1723 cm^{-1} (>C = O group in aliphatic chain), 3367 cm^{-1} (-OH), 1672 cm^{-1} (hydrogen bridge due to hydroxy-carbonyl interaction);[6] semicarbazone, m.p. 229° (Calc. for $C_{15}H_{27}O_2N_3$: C, 64.02; H, 9.67. Found: C, 63.45; H, 9.51)] and ketone (IV) [b.p. 125°/0.6 mm, n_D^{23} 1.4989; λ_{max} 290 mμ (ϵ, 30), band at 1702 cm^{-1} (keto group attached to six membered ring),[7] (Calc. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 78.72; H, 11.10)] identical with the ketone of known absolute configuration[8] (V) obtained from eudesmol (stereochemically correlated with the steroids);[9] identity being further established by comparative infra-red study, $[\alpha]_D^{24}$ + 22° (C, 0.3 in HOAc), m.p. and mixed 221° of the semicarbazone[10] (Calc. for

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5 F. J. Welcher, Organic Analytical Reagents Vol. III, p. 237. Van Nostrand, New York (1949).

6 R. N. Jones, P. Humphries, F. Herling and K. Dobriner, J. Amer. Chem. Soc. 74, 2820 (1952).

7 C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, J. Amer. Chem. Soc. 76, 2969 (1954).

8 W. Klyne, J. Chem. Soc. 3072 (1953).

9 B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, J. Amer. Chem. Soc. 76, 313 (1954).

10 L. Ruzicka, P. A. Plattner and A. Fürst, Helv. Chim. Acta 25, 1364 (1942). We are indebted to Professor Ruzicka for providing us this specimen.

$C_{13}H_{23}ON_3$: C, 65.78; H, 9.77. Found: C, 66.54; H, 9.7). Its configuration was further confirmed by the preparation of dimethyl ester (VI) [b.p. 160°/2.4 x 10^{-2} mm, $[\alpha]_D^{23}$ + 5.9° (C, 1.86 in acetone); (Calc. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 64.9; H, 9.0)] via the dicarboxylic acid obtained through oxidation with $KMnO_4$.

Absolute configuration of the side chain attachment at C(7) was established from the identity of dihydroagarol [b.p. 110-115°/0.5 mm, $[\alpha]_D^{25}$ + 16.6° (C, 2.7 in EtOH); (Calc. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.33; H, 12.70)] with tetrahydrocostol.[11] Further proof in support of this assignment was provided by the preparation of selinane [b.p. 152°/10 mm, n_D^{23} 1.4946; (Calc. for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.10; H, 12.80)] from dihydroagarol via its bromide and subsequent reduction with LiH-$LiAlH_4$ in tetrahydrofuran.[12] The absolute configuration of agarol is thus represented by (VII).

Additional evidence for the presence of allylic moiety in agarol and costol was provided by their metal amine reduction[13] to dihydroselinene (Calc. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 86.52; H, 12.14) and selinene [b.p. 130°/7 mm, n_D^{25} 1.4983, $[\alpha]_D^{26}$ + 22.04° (C, 2.54); (Calc. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.5; H, 11.2)] respectively.

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[11] V. Benešová, V. Sýkora, V. Herout and F. Sorm, Chem. & Ind. 363 (1958). Refer also T. Ukita and S. Nakazawa, Pharm. Bull. (Soc. Japan) 2, 239 (1954).

[12] J. E. Johnson, R. H. Blizzard and H. W. Carhart, J. Amer. Chem. Soc. 70, 3664 (1948).

[13] For pertinent references see A. J. Birch and H. Smith, Quart. Rev. 12, 17 (1958).

Tetrahedron Letters No. 9, pp.18-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE CHEMISTRY OF LUNARIA ALKALOIDS. I.

Peter Bladon, Raphael Ikan,* F. S. Spring, and A. D. Tait

Chemistry Department, The Royal College of Science and Technology, Glasgow

(Received 5 June 1959)

WE wish to report some findings concerning the chemistry of lunarine, which support and augment the conclusions reached recently by Potier and Le Men.[1]

Extraction of the seeds of Lunaria biennis Moench gave lunarine hydrate as needles, m.p. 230-235° (followed by partial solidification and remelting at 270-275° dec.), $[\alpha]_D$+304° (c,0.467 in chloroform) (Found: C, 66.16; H, 7.27; N, 9.61; OMe, 0.0; NMe, 0.0; Equiv., 455.6. Calc. for $C_{25}H_{31}O_4N_3.H_2O$: C, 65.91; H, 7.30; N, 9.23%; Equiv., 455.5). These properties are in good agreement with those reported by Steinegger and Reichstein,[2] Hansen,[3] Boit,[4] and Janot and Le Men.[5]

Janot and Le Men[5] recorded the ultra-violet spectrum of lunarine, and in a recent paper, Potier et al.[6] stated that the spectrum was not changed

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* On leave from the Hebrew University, Jerusalem.

1 P. Potier and J. Le Men, Bull. Soc. Chim. 456 (1959).

2 E. Steinegger and T. Reichstein, Pharm. Acta Helv. 22, 258 (1957).

3 O. R. Hansen, Acta Chem. Scand. 1, 656 (1947).

4 H. G. Boit, Chem. Ber. 87, 1082 (1954).

5 M. M. Janot and J. Le Men, Bull. Soc. Chim. 1841 (1956).

6 P. Potier, J. Le Men and M. M. Janot, Bull. Soc. Chim. 201 (1959).

1959

on making the solution alkaline. We have found that the spectrum of lunarine in alkaline solution is quite different from that in neutral solution. The chief difference is the replacement of the two peaks near 300 mμ by a single maximum at 354 mμ (See Table 1). A surprisingly similar shift to longer wavelengths occurs on changing to a strongly acid solvent. Both these changes are reversible, and are associated with a weak acid and weak basic functions of pK_a' 11.94 and -1.81 respectively. In contrast, protonation of the basic function of lunarine responsible for salt formation (pK_a' 8.02) results in only slight changes in the spectrum.

Lunarine contains a strong band in the carbonyl region of the infra-red spectrum, 1704 cm^{-1}, ascribed by Potier and Le Men[1] to a ketone group. We have made similar findings. Reduction of lunarine with lithium borohydride in methanol gives a mixture of two compounds separable by chromatography. The major product is lunarinol I, m.p. 250-253°, $[\alpha]_D$ +194° (c, 0.443 in methanol). (Found: C, 68.42; H, 7.96; N, 9.55. Calc. for $C_{25}H_{33}O_4N_3$: C, 68.31; H, 7.57; N, 9.56%). Lunarinol I is probably identical with the lunarinol reported by Potier and Le Men.[1] The other product is the isomer, lunarinol II, m.p. 260-270° dec., $[\alpha]_D$ + 166.5° (c, 0.52 in methanol) (Found: C, 68.48; H, 7.33; N, 9.56. $C_{25}H_{33}O_4N_3$ requires C, 68.31; H, 7.57; N, 9.56%).

Neither of this compounds has a peak near 1700 cm^{-1} in the infra-red spectrum, and it is considered that they are stereoisomeric alcohols formed by reduction of a ketone group present in lunarine. In neutral solution their ultra-violet spectra are similar to that of lunarine, but no shift to longer wavelengths occurs on making the solutions alkaline. It may be inferred that the presence of the ketone group is necessary for

this shift to occur, and therefore that in lunarine the ketone group is separated from the main chromophore by an enolizable -CH-group.

TABLE 1. Ultra-violet spectra of lunarine derivatives

	λ_{max} mμ (ϵ)		
	Ethanol	0.1 M NaOH	10 M HCl
Lunarine	208 (29,200) 224 (26,000) 296 (22,100) 315 (17,300)	224 (28,800) 355 (27,500)	236 (24,200) 354 (24,400)
Lunarinol I	210 (25,700) 296 (19,000) 319 (17,400)	215 (59,000) 296 (21,600) 319 (21,300)	234 (21,600) 354 (21,100)
Lunarinol II	216 (34,100) 296 (20,300) 316 (18,300)	218 (55,400) 296 (21,200) 314 (20,400)	238 (24,800) 353 (24,400)
Tosyl-lunarine	205 (35,700) 228 (30,300) 295 (19,500) 320 (16,500)	235 (33,700) 360 (23,200)	212 (29,000) 234 (37,700) 354 (26,600)

Lunarine, on prolonged treatment with toluene-p-sulphonyl chloride in pyridine, gives a monotosyl derivative, m.p. 230-233°, $[\alpha]_D$ + 285° (c, 0.43 in chloroform) (Found: C, 63,03; H, 6.55; N, 6.71; S, 5.42. $C_{32}H_{37}O_6N_3S.H_2O$ requires C, 63.03; H, 6.45; N, 6.89; S, 5.26%) which is recovered unchanged after refluxing with methanolic potassium hydroxide. It is insoluble in dilute acids, which fact shows that the basic nitrogen atom of lunarine is present as a acylable -NH- of $-NH_2$ group. Since only a monotosyl derivative is formed other acylable hydroxyl or -NH- groups are absent. The ultra-violet spectra show that the weak acidic and weak basic functions of lunarine are still present in this derivative.

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We have confirmed the remarkable observations of Steinegger and Reichstein[2] concerning the reaction between lunarine and methyl iodide. The product, m.p. above 330°, $[\alpha]_D$ + 224° (c, 0.3 in water), has an infra-red spectrum differing in only minor respects from that of lunarine hydriodide (Found: C, 51.89; H, 5.79; N, 7.19; OMe, 0.0; NMe, 0.0. Calc. for $C_{25}H_{31}O_4N_3.HI.H_2O$: C, 51.45; H, 5.87; N, 7.20. Calc. for $C_{25}H_{31}O_4N_3.CH_3I.H_2O$: C, 52.25; H, 6.07; N, 7.03; NMe (1), 4.72%). It is reconverted into lunarine by dilute ammonia and there seems little doubt that it is the hydriodide (cf. Boit[4]). This last observation probably indicates that the basic nitrogen atom is sterically hindered.

Pyrolysis of lunarine yields a complex mixture of products, in which we have identified ammonia (as ammonium picrate). This accords well with the recorded formation of ammonia in oxidation,[2] and thermal alkaline[1] degradation reactions, and it is indicative of the presence of an $-NH_2$ group in the molecule.

Hydrolysis of lunarine with hydrochloric acid affords a quantitative yield of the dihydrochloride of an aliphatic diamine $C_5H_{14}N_2$, m.p. 250-253°, $[\alpha]_D$ - 0.05° (c, 0.99 in water). (Found: C, 34.09; H, 8.90; N, 15.49; Cl, 40.75; N-alkyl, 0.0. $C_5H_{14}N_2.2HCl$ requires C, 34.30; H, 9.20; N, 16.00; Cl, 40.50%). This is probably identical with the compound mentioned by Potier and Le Men[1] as being formed by alkaline degradation of lunarine. The corresponding picrate formed needles, m.p. 211-212°.

Comparison of the dihydrochloride of the diamine with authentic samples showed that it was not identical with either pentamethylenediamine

dihydrochloride or diaminoneopentane dihydrochloride,[7] and we tentatively suggest that the diamine has structure (I) for the following reasons. When a solution of

$$(CH_3)_2C(NH_2).CH_2.CH_2.NH_2$$

I

the diamine dihydrochloride is titrated with alkali, the shape of the pH-titration curve shows that there is slight interaction between the amino groups. Comparison with curves obtained with ethylenediamine dihydrochloride, where strong interaction is evident, and with tetramethylenediamine dihydrochloride, where no interaction is revealed, suggests that the two amino groups are separated by three carbon atoms. The fact that the diamine dihydrochloride, which is virtually devoid of optical activity, is formed from the optically active lunarine under conditions in which the possibility of racemization can be discounted, is taken to exclude all asymmetrical structures. Of those structures not excluded by this reasoning, (I), (II), and the meso form of (III), (I) is considered to be the most likely one, since it accounts best for the observation,[5] which we have verified, that lunarine gives negative results in C-methyl determinations. Furthermore, structure (I) is the most

$$CH_3.CH_2.CH(CH_2.NH_2)_2$$

II

$$CH_3.CH(NH_2).CH_2.CH(NH_2).CH_3$$

III

attractive on biogenetical considerations.

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[7] A. Lambert and A. Lowe, J. Chem. Soc. 1517 (1947).

There is abundant evidence in the infra-red spectrum of lunarine for the presence of amide links. It is a reasonable assumption, based on the ease of formation of the diamine by acid hydrolysis, that the C_5-diamine moiety is connected to the remainder of the molecule by one (or possibly two) such links. If we postulate that only one amide link is present here, and that the more hindered $-NH_2$ group of the diamine is free, then an explanation is available for the ready formation of ammonia from lunarine.

Details of this work and of further studies which are in progress will be published later.

Acknowledgements — The authors are indebted to Mr. W. McCorkindale and Miss P. Adams for the microanalyses, Miss E. Bell and Miss M. Black for the ultra-violet spectra, and to Miss J. Goldie for the infra-red spectra. One of them (R.I.) wishes to thank the Friends of the Hebrew University of Jerusalem for a grant.

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HALOGENATIONS SELECTIVES AU MOYEN DES PERHALOGENURES DE PHENYLTRIMETHYLAMMONIUM

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ON sait, depuis les travaux de Rosenmund et al. [1,2] que certains sels de pyridine et quinoléine "transporteurs de brome" peuvent être de précieux agents de bromuration. Parmi ceux-ci, le perbromure de pyridinium ($C_5H_5NH^+Br^-_3$) est devenu un réactif classique[3] généralement utilisé comme source commode de brome, bien qu'il ait été noté[1] que ce réactif a, sur certains composés, un comportement différent de celui du brome libre. Nous avons en particulier montré récemment[4] que le perbromure de pyridinium en solution dans le tétrahydrofuranne permet de bromer sélectivement certains cétals cycliques stéroïdes, même insaturés.

Cependant, le perbromure de pyridinium est un corps difficile à obtenir pur.[5] Alors qu'il doit contenir théoriquement 50% de brome actif, ce titre varie, selon les préparations, et au cours du temps entre 42 et 48% (brome actif titré par iodométrie).

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1 K. W. Rosenmund et W. Kuhnhenn, Ber. 56, 1262 (1923).

2 K. W. Rosenmund, W. Kuhnhenn et W. Lesch, Ber. 56, 2042 (1923).

3 L. F. Fieser, Experiments in Organic Chemistry (3rd. Ed.) p. 65. D. C. Heath, Boston.

4 A. Marquet, H. B. Kagan, M. Dvolaitsky, L. Mamlok, C. Weidman et J. Jacques, C. R. Acad. Sci., Paris 248, 984 (1959).

5 R. Lombard et G. Heywang, Bull. Soc. Chim. 331 (1952).

Nous avons trouvé que le perbromure de phényltriméthylammonium ($C_6H_5N(CH_3)_3^+Br^-_3$) possède les mêmes propriétés que le perbromure de pyridinium sans en avoir les inconvénients. Sa préparation est facile[6] et il est parfaitement stable.[7] Il est très soluble à froid dans le tétrahydrofuranne au sein duquel nous effectuons les bromurations que nous décrivons.

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Ce réactif permet la monobromuration en α des fonctions cétones ou des cétals cycliques, même si la molécule comporte des liaisons éthyléniques ou des noyaux benzéniques activés, alors que le brome libre réagit simultanément sur d'autres parties de la molécule. Nous avons ainsi obtenu avec ce nouveau réactif les divers dérivés bromés antérieurement préparés au moyen du perbromure de pyridinium.[4]

A partir du 3β-acetoxy 20-éthylènedioxy prégna-5,16-diène, nous avons obtenu le 3β-acétoxy 20-oxo 21-bromo prégna-5,16-diène (F. 171-172° $[\alpha]_D = -41°$. Calc. pour $C_{23}H_{31}O_3Br$: C, 63,4; H, 7,2; Br, 18,35. Trouvé: C, 63,4; H, 7,5; Br, 18,5). La structure de ce nouveau composé a été démontrée par sa transformation en 3β,21-diacétoxy 20-oxo prégna-5,16-diène F. 153-155°, $[\alpha]_D = -16°$. (Calculé pour $C_{25}H_{34}O_5$: C, 72,4; H, 8,3. Trouvé: C, 72,2; H, 8,5) lui-même hydrogéné en 3β,21-diacétoxy 20-oxo prégna-5-ène connu.[8]

De même, le méthoxy-6 acétyl-2 naphtalène a été transformé avec un rendement de 80% en méthoxy-6 ω-bromo acétyl-2 naphtalène F. 110-111°

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[6] D. Vorländer et E. Siebert, Ber. 52, 283 (1919).

[7] H. McCombie et T. H. Reade, J. Chem. Soc. 141 (1923).

[8] T. Reichstein et C. Montigel, Helv. Chim. Acta 22, 1213 (1939).

(sel de pyridinium, F_{inst} = 241°. (Calc. pour $C_{18}H_{16}BrNO_2$: C, 60,35; H, 4,50; N, 3,9. Trouvé: C, 59,95; H, 4,75; N, 4,0).

L'anisyl cyclohexyl cétone a fourni également la cétone α-bromée correspondante avec un rendement supérieur à 80% (F. 55-56°. Calc. pour $C_{14}H_{17}O_2Br$: C, 56,6; H, 5,8. Trouvé: C, 56,4; H, 5,8).*

Le bromochlorure de phényltriméthylammonium $(C_6H_5N(CH_3)^+_3BrCl_2^-)$[7] permet de fixer sélectivement Br Cl sur les doubles liaisons, même quand la molécule contient des fonctions cétones ou dioxolanes.

Par action de ce réactif sur l'acétate de cholestéryle, nous avons obtenu avec un excellent rendement le 3β-acétoxy 5α-bromo 6β-chloro cholestane, déjà connu.[9]

De même à partir de l'acide cinnamique nous obtenons un acide β-chloro α-bromo β-phénylpropionique connu.[10]

Le 3β-acétoxy 20-oxo prégna-5-ène fournit avec un rendement de 70% un corps $F_{inst.}$ 195° $[\alpha]_D$ = - 7° (Calc. pour $C_{23}H_{34}O_3BrClO_3$: C, 58,3; H, 7,25. Trouvé: C, 57,9; H, 7,5), très probablement le 3β-acétoxy 5α-bromo 6β-chloro prégnane. Ce produit régénère le 3β-acétoxy 20-oxo prégna-5-ène par action du zinc dans l'acide acétique.

Enfin le 3β-17-diacétoxy-(5α) androsta-16-ène donne avec un rendement quantitatif le 3β-acétoxy 16α-bromo 17-oxo (5α)androstane.[11]

Nous pour suivons actuellement l'étude de ces perhalogénures et de leurs propriétés particulieres.

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* Cette cétone a été transformee par Melle B. Tchoubar en acide anisyl-1 cyclohexane carboxylique-1: voir C. R. Acad. Sci., Paris 201, 277 (1935).

9 J. B. Ziegler et A. C. Shabica, J. Amer. Chem. Soc. 74, 4891 (1952).

10 N. W. Hanson et T. C. James, J. Chem. Soc. 1955 (1928).

11 J. Fajkos, Coll. Czech. Chem. Comm. 312 (1955).

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POSITION OF THE CYCLOPROPANE RING IN AROMADENDRENE

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IN 1953, Birch and Lahey[1] suggested for aromadendrene two alternative structures I and II with the cyclopropane ring in different positions. As aromadendrene on dehydrogenation affords S-guajazulene only, Birch et al. in their recent paper,[2] prefer formula I. In view of the speculative character of this argument, we considered it worthwhile to establish a conclusive proof of the position of the three-membered ring in aromadendrene. We, therefore, carried out the degradation of aromadendrene which enabled us to decide definitely in favour of structure I.

Apoaromadendrone (III)[3] on treatment with perphtalic acid and subsequent hydrolysis of the resulting lactone afforded hydroxy acid IV, m.p. 122.5°, $[\alpha]_D^{20}$ + 6.3° (methanol, c, 3.15), I.R. λ_{max} (dioxan): 1736 cm^{-1} (COOH) and 3490 cm^{-1} (OH). Found: C, 69.77; H, 10.14. $C_{14}H_{24}O_3$ requires: C, 69.96; H, 10.07%. The proof that the tertiary carbon atom was oxidized by Bayer-Villiger procedure has been brought forward by subsequent oxidation of substance IV to the known keto acid $C_{14}H_{22}O_3$ (oxime m.p. 168°).[1]

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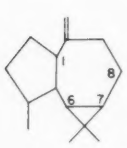
[1] A. J. Birch and F. N. Lahey, Aust. J. Chem. 6, 379 (1953).

[2] A. J. Birch, J. Grimshaw, R. N. Speake, R. M. Gascoigne and R. O. Hellyer, Tetrahedron Letters No. 3, 15 (1959).

[3] L. H. Briggs and W. F. Short, J. Chem. Soc. 2524 (1928).

The methylester of the acid IV on treatment with phenylmagnesium bromide followed by acetylation of the resulting product with acetic anhydride in pyridine, afforded acetoxy derivative of a diphenylcarbinol, m.p. 119-122°, I.R. λ_{max} ($CHCl_3$): 1721, 1260 cm^{-1} (OAc), 3510, 3600 cm^{-1} (OH), 1496, 1600 cm^{-1} (phenyl) and 1377 cm^{-1} (gem. dimethyl on cycloprogane ring[4]). (Found: C, 80.12; H, 8.76. $C_{28}H_{36}O_3$ requires: C, 79.96; H, 8.63%). The carbinol on dehydratation with acetic acid yielded a liquid olefine (I.R. λ_{max}/CCl_4): 1738, 1244 cm^{-1}



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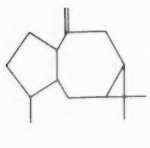

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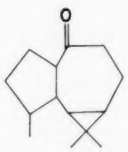

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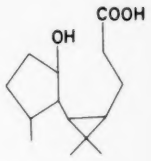

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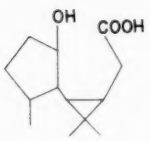

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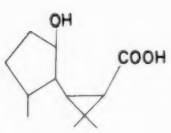

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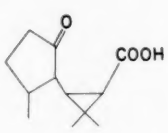
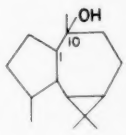


VII



VIII

(OAc), 1496, 1599 cm^{-1} (phenyl) and 1377 cm^{-1} (gem. dimethyl on cyclopropane ring[4]) which was subsequently ozonized. The product of ozonolysis after

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[4] M. Horák and J. Plíva, Coll. Czech. Chem. Comm. In press.

oxidation with hydrogen peroxide in alkaline medium afforded hydroxy acid V, m.p. 153.5°, $[\alpha]_D^{20}$ + 7.7° (alcohol, c, 3.31), I.R. $\lambda_{max}/CHCl_3$): 1672 cm^{-1}, shifted by intermolecular association with hydroxyl group), 3240 cm^{-1} (OH); λ_{max} (dioxan): 1738 cm^{-1} (COOH) and 3492 cm^{-1} (OH). (Found: C, 68.95; H, 9.97. $C_{13}H_{22}O_3$ requires: C, 68.99; H, 9.80%).

The methylester of the acid V submitted to another Barbier-Wieland degradation via the acetoxy diphenylcarbinol (liquid, I.R. $\lambda_{max}/CHCl_3$): 1728, 1258 cm^{-1} (OAc), 3465, 3595 cm^{-1} (OH), 1495, 1600 cm^{-1} (phenyl) and 1378 cm^{-1} (gem. dimethyl on cyclopropane ring[4]) and unsaturated acetoxy derivative (liquid, I.R. $\lambda_{max}/CHCl_3$): 1726, 1255 cm^{-1} (OAc), 1497, 1598 cm^{-1} (phenyl), 1619 cm^{-1} (conjugated double bond) and 1378 cm^{-1} (gem. dimethyl on cyclopropane ring[4]) afforded hydroxy acid VI, m.p. 156°, $[\alpha]_D^{20}$ - 20.5° alcohol, c, 1.47), I.R. $\lambda_{max}/CHCl_3$): 1694 cm^{-1} (COOH); λ_{max}/dioxan): 1726 cm^{-1} (COOH) and 3500 cm^{-1} (OH). (Found: C, 67.79; H, 9.64; H^x, 0.93. $C_{12}H_{20}O_3$ requires: C, 67.89; H, 9.50; H^x, 0.95%). The fact that the three-membered ring in hydroxy acid VI remained untouched came out from the elementary analysis which indicated the normal course of Barbier-Wieland degradation; further the substance did not contain a double bond because it was prepared by ozonolysis and its infra-red spectrum did not exhibit any frequency of ethylenic linkage. The shift of the frequency due to the carbonyl in a carboxyl group (1726 cm^{-1}, dioxan), in comparison with the acid V (1738 cm^{-1}, dioxan) is in accordance with the presence of a cyclopropane ring in α-position to the carboxyl group. The cyclopentane ring of IV, substituted with a hydroxyl group, was maintained in the acid VI as follows from the chromic acid oxidation of the latter to the keto acid VII, m.p. 118° (Found: C, 68.39; H, 8.70. $C_{12}H_{18}O_3$ requires: C, 68.54; H, 8.63%) which in

view of its infra-red spectrum had a keto group in a five-membered ring ($\lambda_{max}/CHCl_3$): 1734 cm^{-1}). (2,4-Dinitrophenylhydrazone: yellow needles, m.p. 241°, found: N, 14.43. $C_{18}H_{22}N_4O_6$ requires: N, 14.35%).

The sequence of degradation ractions outlined above, shows unambiguously in aromadendrene the same location of the cyclopropane ring as in formula I. The identical location of the cyclopropane ring may be ascribed also to some other compounds of the aromadendrene type, the relationship of which with aromadendrene had previously been established. To the compounds mentioned above belong alloaromadendrene, isolated recently in this Laboratory from the oil of Perovskia scrophullariaefolia and Eucalyptus globulus which was characterized as the C_1-epimer of aromadendrene[5b] (cf. also[2]). Further compounds of this group are three stereoisomeric alcohols - globulol,[6] ledol[5,7] and viridiflorol[5b] (cf. also[2]) - which possess the same formula VIII and differ only in configuration on the carbon atoms C_1 and/or C_{10}; their relationship to isomeric aromadendrenes was clarified in our preceding communication.[5b]

[5a] L. Dolejš, F. Šorm and M. Souček, Chem. & Ind. 160 (1959);
[b] L. Dolejš, V. Herout, O. Motl, F. Šorm and M. Souček, Chem. & Ind. 566 (1959); L. Dolejš, O. Motl, M. Souček, V. Herout and F. Šorm, Coll. Czech. Chem. Comm. In press.

[6] A. Blumann, A. R. H. Cole, K. J. L. Thieberg and D. E. White, Chem. & Ind. 1426 (1954).

[7] L. Dolejš, M. Souček, M. Horák and F. Šorm, Chem. & Ind. 494 (1958); Chem. Listy 52, 2188 (1958); Coll. Czech. Chem. Comm. 24, 1353 (1959).

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CONTRIBUTION ON THE STRUCTURE OF CNICIN, THE BITTER PRINCIPLE FROM CNICUS BENEDICTUS L.

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(Received 29 June 1959)

IN a preliminary note,[1] we assigned to cnicin, the bitter principle from Cnicus benedictus L., the molecular formula $C_{20}H_{26}O_7$ and a partial structure I, according to which, cnicine was a dihydroxyguaidienolide esterified with a dihydroxypentenoic acid, not characterized in detail. In view of our recent results, however, cnicin is a monocyclic trihydroxyester-lactone of molecular formula $C_{20}H_{28}O_7$* and structure II or III; it belongs thus to the group of sesquiterpenic lactones with a ten-membered ring in the molecule. Cnicin is esterified by α,β-bis-(hydroxymethyl)acrylic acid.

The volatile C_5-acid, reported in our preceding paper,[1] obtained from cnicin after hydrogenolysis and subsequent saponification, afforded the p-bromophenacyl ester of m.p. 53°, underpressed on admixture of the corres-

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* Elemental analyses of this substance which, because of its unstability, can be hardly prepared in a pure state, did not enable us to decide unambiguously between formulae $C_{20}H_{26}O_7$ and $C_{20}H_{28}O_7$. The first alternative, i.e. the formula with the lower hydrogen content might be explained only by the fact that instead of a dihydroxy-acid a hydroxy-aldehydo-acid, present in a cyclo-hemiacetal form, is bond to cnicin.

[1] M. Suchý, V. Herout and F. Sorm, Chem. & Ind. 517 (1959).

ponding derivative of authentic methylethylacetic acid. On hydrogenation, cnicin afforded a product of the molecular formula $C_{20}H_{32-34}O_7$ and m.p. 146° which on subsequent hydrolysis yielded another product of reduction of the acid present in cnicin, which was characterized as a hydroxy-lactone IV of molecular formula $C_5H_8O_3$. Now, we have obtained its crystalline 3,5-dinitrobenzoate of m.p. 122° (Found: C, 46.82; H, 3.24; N, 9.11% : Calc. for $C_{12}H_{10}O_8N_2$: C, 46.46; H, 3.25; N, 9.03%). The above melting point agrees with that of the corresponding derivative of the known α-hydroxymethyl-γ-butyrolactone (IV).[2] The location of the ethylenic linkage of the original acid III, present in cnicin in the form of an ester, followed from its allylic position to both hydroxyl groups and further from its α,β-position to the esterified carboxyl group.

The proof of the carbon skeleton of cnicin has been established by a series of further experiments. On hydrogenation with PtO_2 in methanol, cnicin afforded a mixture which was saponified and the resulting neutral product separated by chromatography on alumina. The last eluates afforded two crystalline compounds of m.p. 118°, $[\alpha]_D^{20}$ + 4.4° (chloroform, c = 1.94) (V) and m.p. 112°, $[\alpha]_D^{20}$ - 28.7° (ethanol, c = 2.08) (VI). (Found for V: C, 66.66; H, 9.66% ; for VI: C, 66.51; H, 9.61% : Calc. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%). The infra-red spectra of compounds V and VI differ in details only and exhibit the same absorption bands due to a carbonyl group in γ-lactone (1764 cm^{-1}) and to a hydroxyl group (3380-3470 cm^{-1} and 3625-3630 cm^{-1}) (measured in chloroform solution). Both compounds are

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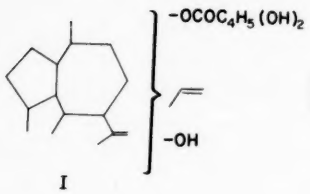
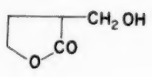
[2] W. J. McGraw, U.S. 2,624.723 Jan. 6, 1953.

thence monocyclic dihydroxy-lactones.

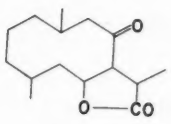
On treatment with chromic acid in acetic acid, compounds V and VI afforded two different lactone-keto acids; m.p. 220°, $[\alpha]_D^{20}$ - 19.4° (ethanol, c = 1.74) (VII) and m.p. 188° $[\alpha]_D^{20}$ ± 0° (ethanol, c = 0.7) (VIII). (Found for VII: C, 63.94; H, 8.00% ; for VIII: C, 63.49; H, 7.90% : Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%). Infra-red spectra of the acids VII and VIII exhibited absorption bands due to a carbonyl group in a γ-lactone (1781 or 1788 cm^{-1} resp.) and to a carboxyl group (1731 of 1736 cm^{-1} resp.).



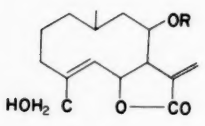
I



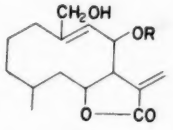
IV



IX



II



III

II, III: R = -OCOC (CH$_2$OH)=CHCH$_2$OH

The formation of a carboxyl group in the course of oxidation of dihydroxy lactones V and VI constitutes the proof that one of the hydroxyl groups of

the sesquiterpenic lactone moiety of cnicin is primary in character. This explains the lower values for the C-methyl group (0.86) obtained by the Kuhn and Roth method. From the presence of an absorption band at 1700 cm^{-1}, due to a keto group, in the infra-red spectrum of VII and VIII it follows that the second hydroxyl group present in diol-lactones V and VI is secondary in character and is located on a medium-sized ring.

The non-crystalline chromatographic fraction which preceded fractions containing compounds V was oxidized with chromic acid in acetic acid. The reaction mixture obtained afforded, besides some lactone-keto acid VII, a neutral material of m.p. 135°. The latter, according to the mixed melting point and infra-red spectrum, was found to be identical with the keto-lactone, prepared from arctiopicrin. The constitution of the keto-lactone, expressed by formula IX, was elucidated[3,4] in this Laboratory.

All these findings constitute the proof that cnicin is a new lactone belonging to the sesquiterpenic germacrane type with a ten-membered ring in its molecule. The keto-lactone IX was obviously formed on oxidation of hitherto non-isolated hydroxy-lactone X which resulted after hydrogenolysis of the primary hydroxyl group present in original cnicin. This also proves one of the double bonds of cnicin to be in allylic position to the primary hydroxyl group.

The mixture obtained on hydrogenation of cnicin afforded on subsequent oxidation acidic material only, the infra-red spectrum of which did not exhibit

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[3] M. Suchý, V. Herout and F. Šorm, Croatica Chem. Acta 29, 247 (1957).

[4] M. Suchý, V. Herout and F. Šorm, Chem. Listy 52, 2110 (1958); Coll. Czech. Chem. Comm. 24, 1542 (1959).

frequencies characteristic for a keto group. The above acidic material was saponified and the obtained product oxidized by means of chromic acid to yield lactone-keto acid VI. From the above finding it follows that the secondary hydroxyl group on C_8 in cnicin is esterified by the moiety of acid III.

Cnicin, on oxidative degradation by nitric acid catalysed with vanadium pentoxide afforded acidic material from which, by means of modified preparative paper chromatography[5,6] four dicarboxylic acids were isolated in a pure state: succinic acid (m.p. 183°), methylsuccinic acid (m.p. 112°), α-methylglutaric acid (m.p. 79°) and α-methyladipic acid. The latter was characterized as its S-benzylthiuronium salt, m.p. 169°, undepressed on admixture of an authentic sample, and further by means of the infra-red spectrum of its dimethyl ester. In view of paper chromatography, the mixture of acids contained a dicarboxylic C_8 acid which has not yet been identified.

All these findings indicate that cnicin possesses one of the two alternative formulae II and III. Work on the structure and determination of the absolute configuration of cnicin is in progress. The results will be published in full detail in Collection of Czechoslovak Chemical Communications.

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[5] V. Šanda, Ž. Procházka and H. LeMoal, Chem. Listy 52, 1546 (1958); Coll. Czech. Chem. Comm. 24, 420 (1959).

[6] V. Sýkora, V. Herout and F. Šorm, Chem. Listy 52, 1314 (1958); Coll. Czech. Chem. Comm. 23, 2181 (1958).

Tetrahedron Letters No. 10, pp. 10-12, 1959. Pergamon Press Ltd. Printed in Great Britain.

ZUR STRUKTUR DER LÖSUNGEN - III.[1]

RACEMAT-SPALTUNG DURCH EIN OPTISCH AKTIVES LÖSUNGSMITTEL

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Chemisches Laboratorium der Universität Freiburg i.Br.

(Received 6 July 1959)

DIE Literatur[2] enthält eine Reihe exakt fundierter Angaben, nach denen in optisch aktiven Solventien Löslichkeit, Molvolumen, Viscosität u.ä. für darin gelöste optische Antipoden gleich sind. In einigen ebenso sorgfältig studierten Fällen wurden jedoch signifikante, wenn auch geringe Differenzen für die Antipoden gefunden: so vermochten Buchanan und Graham[3] die Antipoden eines (mit Absicht leicht racemisierbar gewählten) atropisomeren Racemates durch ein aktives Lösungsmittel geringfügig zu aktivieren (erreichtes $\alpha = + 0{,}2^{0}$ bzw. $- 0{,}15^{0}$).

Die Widersprüche in der Literatur klären sich unserer Meinung nach weitgehend, wenn man postuliert, dass zur Erzielung sterisch genügend differenzierter und deshalb in der Löslichkeit differierender Solvate die Moleküle von Substrat und Solvens an wenigstens zwei Punkten eng verknüpft

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[1] II. Mitt.: R. Worthmann und A. Lüttringhaus, Makromol. Chem. 18/19, 522 (1956).

[2] Übersicht: K. Freudenberg, Stereochemie S. 555 ff. Leipzig und Wien (1933), sowie 3.

[3] C. Buchanan und S. H. Graham, J. Chem. Soc. 500 (1950).

sein sollten,[4] z.B. durch H-Brücken.[5] So wird verständlich, dass einfache optisch aktive Kohlenwasserstoffe, Halogenide oder Alkohole zur optischen Aktivierung auf diesem Wege als Substrat wie als Lösungsmittel im allgemeinen versagt haben; ebenso, dass symmetrisch, H-Brücken-aktive Lösungsmittel die Effekte verwischen: d- und l-Ammoniumtartrat haben in d-Glucose-Wasser die gleiche Löslichkeitskurve.[6]

Auf Grund dieser Arbeitshypothese wählten wir als erste Substrat-Beispiele rac. 2,3-Dibrombutandiol-(1,4) (I) und rac. Bis-(4-pyridyl)-glykol (II). Beide liessen sich durch einfaches Umkristallisieren aus rechtsdrehendem D-Di-isopropyl-tartrat (Dipt) sogleich aktivieren.

Spaltung von I: 20 g I in 20 ml Dipt bei + 90°C gelöst: Nach 24 Stunden bei + 18°C (mit rac. I geimpft!): 6 g I, $[\alpha]_D^{20}$ - 1,79°; diese aus 10 ml Dipt (8 Tage bei 18 - 20°): 1,9 g I, $[\alpha]_D^{20}$ - 8,0°; diese aus 3,5 ml Dipt (14 Tage bei 18 - 20°): 163 mg I, $[\alpha]_D^{20}$ - 37,8° (7% in Methanol).

Die Kristalle von I (wegen der Viscosität des Dipt zwar langsam erscheinend, aber deshalb gut ausgebildet), durch einfaches Abfiltrieren und Waschen mit Methylenchlorid isoliert, enthielten kein Kristall-Lösungsmittel: $C_4H_8Br_2O_2$ (247,9) Ber. C 19,38 H 3,25; Gef. C 19,66 19,60 H 3,33 3,38.

Aus den Mutterlaugen wurden durch Fällen mit Methylenchlorid positiv drehende I-Fraktionen erhalten. Inerte Zusatz-Solventien wie Benzol ver-

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[4] Ähnliche Bedingungen erscheinen für Racematspaltung an aktiven Adsorbentien erforderlich: H. Krebs et al., Chem. Ber. 89, 1875 (1956); C. E. Dalgliesh, J. Chem. Soc. 3940 (1952).

[5] Auf deren etwaige Bedeutung weisen Buchanan und Graham hin: l.c.[3]

[6] H.C. Cooper, Amer. Chem. J. 32, 255 (1900).

hindern die optische Aktivierung nicht.

Spaltung von II: 1 g II in 15 ml Dipt 1 Stunde auf 95° erwärmt, von Ungelöstem filtriert, 3 Wochen bei + 18 - 20° gehalten: 63 mg II, $[\alpha]_D^{21}$ + 5,77° (3,2% in Methanol). Optisch reines (+) II hat $[\alpha]_D^{20}$ + 36,5° in Methanol.[7] Näheres vergl.[8]

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[7] A. Lüttringhaus und D. Berrer, Angew. Chemie 70, 439 (1958).
[8] D. Berrer, Dissertation Freiburg/Brsg. (1959).

Tetrahedron Letters No. 10, pp.13-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

GEMISCHTE CARBONYLKOMPLEXE DES Cr^0 UND DES Mo^0 MIT ORGANO-STICKSTOFFVERBINDUNGEN

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NACH Hieber und Muhlbauer[1] können aromatische, mesomeriefähige Amine wie Pyridin (Py) und Phenanthrolin (Phol) als Liganden in komplexen Carbonylverbindungen von Metallen der 6. Gruppe auftreten wie z.B. $(Py)_3Mo(CO)_3$, $(Phol)Mo(CO)_4$; auch das carbonylfreie Tris-dipyridyl-Chrom wurde kürzlich von Herzog und Schon[2] gewonnen.

Die Untersuchung, in welchem Bereich allgemein stickstoffhaltige organische Verbindungen CO aus Cr- und Mo-hexacarbonyl verdrängen können, hat vorerst folgendes ergeben: α-Alkylpyridine wie α-Picolin oder 2,6-Lutidin reagieren nicht. Chinolin (Chin) liefert das gelbbraune $(Chin)Mo(CO)_5$ (I), 8-Aminochinolin (Amchin) das gelbbraune $(Amchin)Cr(CO)_4$ (II), das leicht reagierende α,α'-Dipyridyl (Dipyr) die leuchtend roten $(Dipyr)Cr(CO)_4$ (III) und $(Dipyr)Cr(CO)_4$ (IV). 2-Methylpyrazin (Mepyz) verdrängt 2CO und bildet die roten $(Mepyz)_2Cr(CO)_4$ (V) und $(Mepyz)_2Mo(CO)_4$

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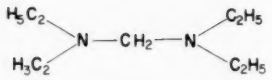
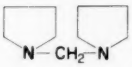
[1] W. Hieber und F. Mühlbauer, Z. Anorg. Chem. 221, 337, 349 (1935).

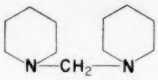
[2] S. Herzog und W. Schön, Z. Anorg. Chem. 297, 323 (1958).

(VI) (λ_{max} 285, 315 und 415 mμ in Dibutyläther).

Von nichtaromatischen Aminen verdrängten die Methylen-bis-amine

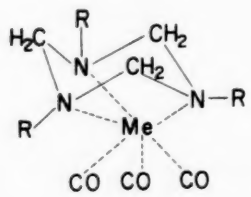






in $Mo(CO)_6$ zwei CO und bildeten die gelben Komplexe (Diamin)$Mo(CO)_4$ VII, VIII und IX (λ_{max} 301 und 405 mμ).

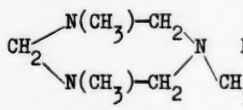
Auch mit Hexahydro-triazinen gelang die Komplexbildung gut. Wir konnten folgende 6 Komplexe aus den Hexacarbonylen gewinnen, wobei selbst der Cyclohexylrest nicht hinderte:



	Me	R	Farbe
X	Cr	CH_3	gelb
XI	Cr	C_2H_5	orange
XII	Cr	C_6H_{11}	gelb
XIII	Mo	CH_3	gelb
XIV	Mo	C_2H_5	gelb
XV	Mo	C_6H_{11}	gelb

Alle sind kristallin und schwerlöslich. In Äther oder Petroläther suspendiert, nehmen XIII und XIV schon bei Normaldruck und -Temperatur CO auf.

XIII addiert 2CO zu



, XIV 3CO unter

Ruckbildung von $Mo(CO)_6$. Dagegen ist XV stabil gegen CO unter diesen Bedingungen, offenbar schirmen die C_6H_{11} ab.

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Urotropin (Utr) reagierte nur mit einem N-Atom zum gelben $(Utr)MoCO_5$ (XVI) (λ_{max} 252, 289, 387 mμ in Dibutyläther).

Darstellung stets durch Erhitzen von Amin und Hexacarbonyl auf 130 - 150° unter N_2, z.T. in Dibutyläther oder Ligroin. Auch aus $(Pyr)_3Mo(CO)_3$ + Amin gelang die Darstellung, z.B. von XIII.

Die Komplexe sind kristallin, haben aber keinen Schmelzpunt, da sie sich oberhalb 150° zersetzen. III, IV, VII, VIII, IX und XVI sind luftbestandig, die übrigen zersetzen sich bald, z.T. sogar langsam in N_2-Atmosp. re.

I.R.-Spektren: Zum Unterschied von den Hexacarbonylen, die nur eine Carbonylbande bei 2000 cm^{-1} aufweisen, haben alle erwähnten Komplexe mehrere Carbonylbanden; ihre Lage und Zahl scheint fur die Anzahl der CO-Gruppen charakteristisch zu sein:

Verbindung	CO-Banden in cm^{-1} [3]					
$Cr(CO)_6$, $Mo(CO)_6$		2000				
Komplex mit 5 CO	2105	2000	1940	1890		
Komplex mit 4 CO		2020		1900	1830	
Komplex mit 3 CO				1900	1785	1770

[3] Die angegebenen Werte sind Mittelwerte. Schwankungen bei den einzelnen Komplexen bis etwa ± 15 cm^{-1}.

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MOLECULAR STRUCTURE AND CONFORMATION OF SOME DIHALOGENODIOXANES[1]

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(Received 6 July 1959)

IN recent years the properties and the conformational relationships of some dihalogenocyclohexanes and dihalogenodecalins have been studied in this laboratory.[2,3,4] In the present communication we summarize the results obtained in extending the investigations to halogeno-substituted dioxanes.

Monochlorodioxane, the known dihalogenodioxanes and one 2,3,5,6-tetrachlorodioxane were synthesized (see Table 1) and studied.

The following methods were employed for the investigation of the conformational characteristics of the dihalogenodioxanes:

(1) Dipole moments were calculated from measurements in dilute solutions

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[1] Details will be published in the thesis of C. Altona, Leiden and in forthcoming publications in Rec. Trav. Chim. The results of the X-ray analyses will be published in Acta Cryst.

[2] W. Kwestroo, F. A. Meyer and E. Havinga, Rec. Trav. Chim. 73, 717 (1954).

[3] W. Kwestroo, Thesis, Leiden (1954).

[4] J. A. van der Linden, Thesis, Leiden (1958).

TABLE 1. Dipole moments of some halogeno-substituted dioxanes

XX	Compound	Melting point	Dipole moment in benzene	(Debyes) in CCl_4
I	Monochlorodioxane[5]		2.24	2.28
II	Trans-2,3-dichlorodioxane[6]	31	1.63	1.62
III	Trans-2,3-dibromodioxane[7]	74	1.90	1.86
IV	Cis-2,3-dichlorodioxane[6]	54	3.06	3.00
V	Trans-2,5-dichlorodioxane[8]	124	0.6	0.6
VI	Trans-2,5-dibromodioxane[9]	86 - 100 (decomp.)	0.8	
VII	2,3,5,6,-Tetrachlorodioxane[10]			

in benzene and carbon tetrachloride, using the extrapolation formulas of Halverstadt and Kumler.[11]

(2) Infra-red absorption spectra were obtained from the compounds in the solid state (KBr-disks) and from solutions in carbon disulphide; the spectrum of III was also measured in cyclohexane and the spectrum of II in cyclohexane and nitromethane.

(3) Raman spectra were taken of solutions of II, III and IV in solvents with dielectric constants varying from 2.1 to 37.5.

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[5] R. K. Summerbell and L. N. Bauer, J. Amer. Chem. Soc. 57, 2364 (1935).

[6] R. K. Summerbell and H. E. Lunk, J. Amer. Chem. Soc. 79, 4802 (1957).

[7] H. C. Dehm, J. Org. Chem. 147 (1958).

[8] L. A. Bryan, W. M. Smedley and R. K. Summerbell, J. Amer. Chem. Soc. 72, 2206 (1950).

[9] R. K. Summerbell and L. K. Rochen, J. Amer. Chem. Soc. 63, 3241 (1941).

[10] M. Udicke and W. Stumpf, Naturwissenschaften 40, 363 (1953).

[11] I. F. Halverstadt and W. D. Kumler, J. Amer. Chem. Soc. 64, 2988 (1942).

(4) X-ray diffraction patterns were taken of single crystals of III, IV, V and VII (see Table 2).

TABLE 2. Dimensions of the unit cells in Ångstrom units and space-groups of some halogenodioxanes

Dioxane derivatives		a	b	c	α	β	γ	n	Space-group
III	Trans-2,3-dibromo-	5.68	7.63	16.02	90	90	90	4	$P2_12_12_1$
IV	Cis-2,3-dichloro-	4.52	10.75	13.12	90	90	90	4	$P\,2_1/n$
V	Trans-2,5-dichloro-	4.58	5.46	6.56	86	102.5	107	1	P 1
VII	2,3,5,6-tetrachloro-	6.70	7.60	$\frac{7.52}{\sin\beta}$	90		90	2	$P\,2_1/c$

The analyses of the structure of III and V are in the stage of refinement; they confirm that both compounds are trans-substituted and that the dioxane ring has the chair conformation. To our surprise the halogen atoms of both compounds were found to occupy axial positions.

As is well known, the trans-1,2- and the trans-1,4-dihalogeno-cyclohexanes occur in solution as an equilibrium mixture consisting mainly of two conformations, the diaxial (aa) and the diequatorial (ee) chair conformations. This equilibrium varies with the solvent, as is evident from the solvent-dependent dipole moments in the case of the 1,2-trans-substituted compounds and from the solvent-dependent Raman spectra and infra-red absorption spectra of these substances.[2,3,12-16]

[12] K. Kozima and T. Yoshino, J. Amer. Chem. Soc. 75, 166 (1953); K. Kozima, K. Sakashita and S. Maeda, J. Amer. Chem. Soc. 76, 1965 (1954).

The trans-substituted dihalogenodioxanes differ in these aspects from the cyclohexane analogues. The dipole moment appeared to be independent of the solvent. The infra-red spectra of these compounds in solution - regardless of the solvent - are in all cases identical with those of the crystals. The Raman spectra were also found not to vary with the solvent and to be practically identical with those obtained from the crystalline material.

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No indications were found, then, for the occurrence of more than one conformation. We tentatively conclude that the molcules of the trans-dihalogenodioxanes show a strong preference for one of the possible conformations.

Taking into consideration that, according to the X-ray analyses, in solid III and V the halogen atoms are in aa positions, that the dipole moments of II and III do not differ appreciably and that the infra-red spectra of V and VI bear a close resemblance, we feel safe in concluding that the trans-2,3-dihalogeno- and the trans-2,5-dihalogenodioxanes occur in solution as well as in the solid state in the diaxial chair conformation.

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[13] A. Tulinskie, A. DiGiacomo and C.P. Smyth, J. Amer. Chem. Soc. 75, 3552 (1953).

[14] P. Bender, D. L. Flowers and H. L. Goering, J. Amer. Chem. Soc. 77, 3463 (1955).

[15] P. Klaeboe, J. J. Lothe and K. Lunde, Acta Chem. Scand. 11, 1677 (1957).

[16] For an early discussion of infra-red data see also: M. Larnaudie, C. R. Acad. Sci., Paris 326, 909 (1953). The results of investigations on the conformations of cyclohexane derivatives in the gaseous state by electron diffraction were summarized by O. Hassel, Research 3, 504 (1950).

Cis-2,3-dichlorodioxane (IV) probably has the ea conformation, in accordance with the value for the dipole moment that is practically the same as that found for cis-1,2-dichlorocyclohexane (3.13 D[3]).

The dipole moments of II and III are somewhat higher than might be expected for a purely diaxial conformation. More data will be needed before a choice can be made between the several possible causes for this phenomenon.

As to the reasons why the halogen atoms preferentially occupy axial positions in the case of dihalogenodioxanes, it might be argued that with such compounds the interaction between the electrons of an equatorial halogen atom and those of the oxygen atom is relatively unfavourable. Furthermore, the number of axial hydrogen atoms that cause steric hindrance is, of course, smaller in the derivatives of dioxane than in the substituted cyclohexanes.

Tetrahedron Letters No. 10, pp. 21-22, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

THE STEREOCHEMISTRY OF ISOPHYLLOCLADENE

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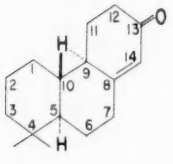
(Received 7 July 1959)

ISOPHYLLOCLADENE has been converted into podocarp-8(14)-en-13-one (I), identical with a sample prepared from manool.[1] Hence isophyllocladene must possess the "normal" trans A/B ring junction, since the reactions employed do not permit the possibility of inversion at these centres. As Djerassi[2] has already pointed out that only one structure possessing this ring fusion is permitted by rotatory dispersion evidence, isophyllocladene must be as depicted in (II).



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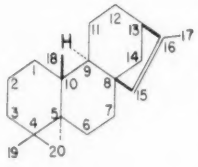

II

[1] J. R. Hosking, Ber. 69, 780 (1936).

[2] C. Djerassi, M. Cais and C. A. Mitscher, J. Amer. Chem. Soc. 81, 2386 (1959).

Hydroxylation of isophyllocladene with osmium tetroxide gave the known dihydro-15,16-dihydroxyphyllocladene.[3] When this was oxidised with lead tetracetate, 13β-acetyl-8β-aldehydopodocarpane was formed, m.p. 138-140°, $[\alpha]_D$ - 39°. The derived dioxime was dehydrated with acetic anhydride to give the oxime of 13β-acetyl-8β-cyanopodocarpane, m.p. 195-197°, $[\alpha]_D$ - 13°.

The parent ketone was regenerated and subjected to the action of pertrifluoroacetic acid. After hydrolysis of the resulting acetate, 8β-cyano-13-hydroxypodocarpane was produced, m.p. 95-115°. No attempt was made to separate this mixture of 13-hydroxy-isomers, but oxidation with chromium trioxide gave 8β-cyano-13-oxopodocarpane, m.p. 160-161° (with prior melting and resolidification at 153-154.5°), $[\alpha]_D$ + 33°. When this substance was distilled from powdered potassium hydroxide at 120°/0.01 mm, hydrogen cyanide was eliminated, giving podocarp-8(14)-en-13-one, m.p. 64-66°, $[\alpha]_D$ + 45°, λ_{max} (MeOH) 242.5 mμ, ϵ = 16,000. A specimen of the same material prepared from manool had m.p. 64-66°, $[\alpha]_D$ + 49°, λ_{max} (MeOH) 242.5 mμ, ϵ = 16,400. The infra-red spectra of the two samples in CCl_4 were identical. All rotations were measured in chloroform at 18°, and satisfactory analyses have been obtained for all the compounds reported.

The authors express their thanks to Professor R. A. Raphael for his advice and encouragement.

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[3] C. W. Brandt, New Zealand J. Sci. Technol. 34B, 46 (1952).

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Tetrahedron Letters No. 11, pp. 1-3, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE MOLECULAR STRUCTURE OF ASPIDOSPERMINE

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Department of Chemistry, University College of North Staffordshire, Keele

(Received 3 July 1959)

1959

THE alkaloid aspidospermine obtained from the bark of Aspidosperma quebracho blanco and first studied by Ewins[1] in 1914 has been the subject of active chemical study since 1947. It has proved to be a member of that increasingly large body of natural products whose molecular structure eludes unambiguous determination by degradative methods.

The molecular structure has now been unequivocally established by a three-dimensional X-ray analysis of crystals of (-)-aspidospermine-N(b)-methiodide kindly supplied by Dr. G. F. Smith of Manchester University. The crystals belong to the orthorhombic system, $\underline{a}$ = 24.3, $\underline{b}$ = 8.5, $\underline{c}$ = 11.1 A, space group $P2_12_12_1$, four molecules, $C_{23}H_{33}N_2O_2I$, to the unit cell.

The iodide ions were used for establishing phases by the usual heavy-atom technique and three-dimensional electron density plots were calculated on DEUCE through the courtesy of the English Electric Co. Ltd. Because of the slow refinement of noncentric crystal structures due attention was paid in the first instance to the four currently acceptable molecular structures. Although the analysis could have proceeded without this

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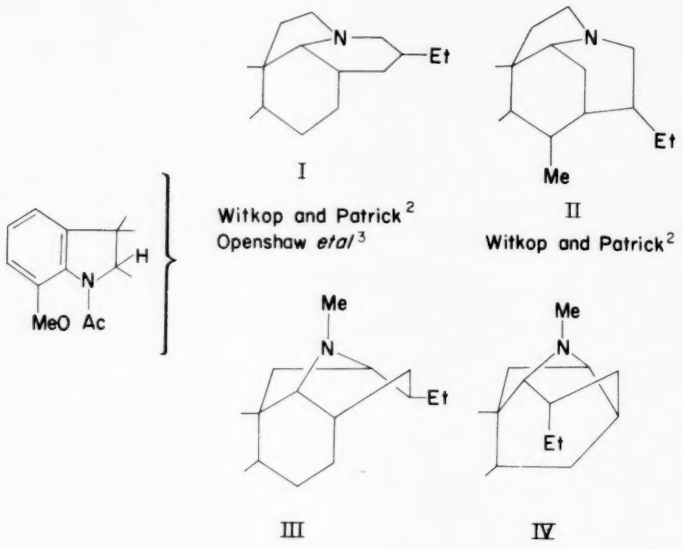
[1] Ewins, J. Chem. Soc. 2738 (1914).

knowledge the refinement was considerably speeded up by its use. At the commencement of the structure analysis the structures borne in mind were:



Towards the end of the refinement Conroy and co-workers,[5] unaware of our X-ray work, withdrew their two molecular structures III and IV which alone contain N-methyl groups.

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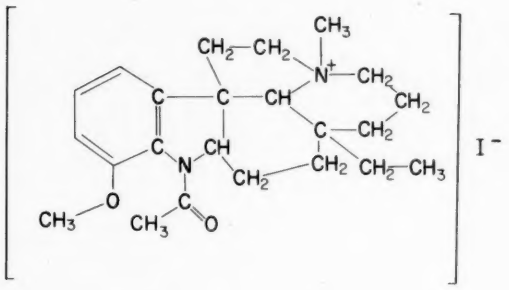
[2] Witkop and Patrick, J. Amer. Chem. Soc. 76 5603 (1954).

[3] Openshaw, Smith and Chalmers, 13th International Congress on Pure and Applied Chemistry. Abstracts, p. 223 (1953).

[4] Conroy, Brook, Rout and Silverman, J. Amer. Chem. Soc. 79, 1763 (1957).

[5] Conroy, Brook, Rout and Silverman, J. Amer. Chem. Soc. 80, 5178 (1958).

X-ray analysis has proved that the major part of the structure is correctly given by I above. The ethyl group however is not located as shown but is attached to one of the two quaternary carbon atoms in the hexahydrocarbazole system. The molecular structure of the methiodide is:



A full account of the analysis and of the detailed stereochemistry will be published elsewhere.

Tetrahedron Letters, No. 11, pp. 4-11,1959. Pergamon Press Ltd. Printed in Great Britain.

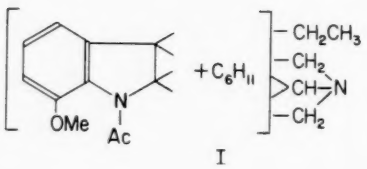
ON THE STRUCTURE OF ASPIDOSPERMINE[1]

Harold Conroy, Peter R. Brook and Yaacov Amiel

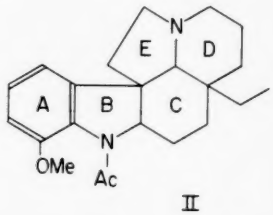
Dept. of Chemistry, Yale University, New Haven, Conn.

(Received 27 July 1959)

IN Part II[2] we outlined the development of the partial structural formula (I) for the alkaloid aspidospermine. The additional chemical evidence



I



II

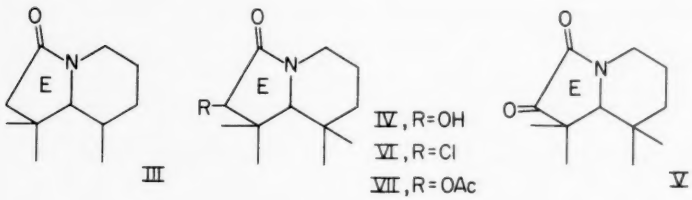
described in this Letter confirms those conclusions and has a considerable further bearing on the structure. While mainly limited to elucidation of the nature of rings D and E enclosing the basic nitrogen (N_b), our results

[1] Part III of a series. Contribution numbered 1570 from the Sterling Chemistry Laboratory at Yale University.

[2] H. Conroy, P. R. Brook, M. K. Rout and N. Silverman, J. Amer. Chem. Soc. 80, 5178 (1958).

to that extent are fully in support of the complete formulation (II) which is deduced by Mills and Nyburg on the basis of their recent elegant X-ray crystallographic studies and discussed in an accompanying communication.

Chromium trioxide-pyridine oxidation of the alkaloid gave a neutral fraction, separable into three components by chromatography on Florisil. The first eluted was aspidospermine lactam-B (III), m.p. 115° from benzene (Found: C, 75.18; H. 7.70; N, 6.19. $C_{22}H_{28}O_3N_2 \cdot C_6H_6$ requires: C, 75.30; H, 7.67; N, 6.27.)[3] with $\nu\nu_{max}$ 1652 (N_a-acetyl) and 1680 cm^{-1} (five-membered lactam). Aspidospermine lactam-C (IVa) moved more slowly in the



III

IV, R=OH
VI, R=Cl
VII, R=OAc

V

chromatogram; it was crystallized from benzene and gave the m.p. 228-230° (transition at 147°) (Found: C, 72.59; H, 7.22; N, 6.04. $C_{22}H_{28}O_4N_2 \cdot C_6H_6$ requires: C, 72.70; H, 7.41.; N, 6.06.)[3] and $\nu\nu_{max}$ 1692 (lactam carbonyl) and 3305, 3520 cm^{-1} (hydroxyl). Lactam-D (V), with intermediate mobility

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[3] The inclusion of benzene in these stable crystalline solvants was shown independently of the analysis in each case by the intense singlet benzene absorption in the NMR spectrum of the analytical sample.

in the chromatogram, has the m.p. 249° from benzene (Found: C, 72.84; H, 7.05; N, 6.04. $C_{22}H_{26}O_4N_2 \cdot C_6H_6$ requires: C, 73.02; H, 7.00; N, 6.08.)[3] and gives the very characteristic infrared doublet $\nu\nu_{max}$ 1721 and 1770 cm^{-1} of the five-membered α-keto-lactam[4] as well as ν_{max} 1660 cm^{-1} (N_a-acetyl). Lactam-D oxime, m.p. 261° from benzene (Found: C, 68.06; H, 6.97; N, 9.92. $C_{22}H_{27}O_4N_3 \cdot \frac{1}{3}C_6H_6$ requires: C, 68.06; H, 6.90; N, 9.92.)[3] formed rather slowly. Potassium borohydride reduction of the ketonic carbonyl of V gave the α-hydroxylactam (IVb), m.p. 247° from ethyl acetate (Found: C, 69.08; H, 7.58; N, 7.91. $C_{22}H_{28}O_4N_2$ requires: C, 68.72; H, 7.34; N, 7.29.) with $\nu\nu_{max}$ 1654 (N_a-acetyl) 1697 (lactam carbonyl) 3310 and 3510 cm^{-1} (hydroxyl). Lactam-C and the borohydride reduction product are epimeric at the hydroxylated carbon. Lactams -B and -C were interrelated by conversion of -C to the α-chlorolactam (VI), m.p. 294-296°, (ν_{max} 1718 cm^{-1}; Found: C, 65.46; H, 6.77; Cl, 8.55. $C_{22}H_{27}O_3N_2Cl$ required: C, 65.68; H, 6.75; Cl, 8.80) with phosphorus oxychloride followed by zinc dust reduction of VI to III. Absence of any skeletal change in the oxidation was shown by reduction of lactam-B to N_a-ethyldeacetylaspidospermine[5] with lithium aluminum hydride.

The 60 mc/sec NMR spectrum[6] of lactam-B shows a well resolved two proton nonequivalence quartet centered at $\tau = 7.63$ with $J = 16.2$ cps,

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[4] Thus 1,5-diphenyl-2,3-diketopyrrolidine absorbs at 1712 and 1770 wavenumbers [H. H. Wasserman and R. C. Koch, Chem. & Ind. 428 (1957); Cf, P. L. Southwick, E. P. Previc, J. Casanova, Jr. and E. H. Carlson, J. Org. Chem. 21, 1087 (1956).].

[5] B. Witkop and J. B. Patrick, J. Amer. Chem. Soc. 76, 5603 (1954).

[6] NMR spectra were measured on a Varian Associates instrument with 99.5% deuteriochloroform as solvent and tetramethylsilane as internal reference.

absent in the corresponding regions of the curves for aspidospermine, for lactam-C or for lactam-D, which must be ascribed to the methylene immediately adjacent to the lactam-B carbonyl. The NMR spectrum of lactam-C O-acetate (VII), m.p. 211° [$\nu\nu_{max}$ 1706 (lactam carbonyl) and 1754 cm^{-1} (O-acetyl); Found: C, 67.41; H, 7.04; N, 6.68. $C_{24}H_{30}O_5N_2$ requires: C, 67.58; H, 7.09; N, 6.57.)], is marked by a sharp one proton singlet peak at $\tau = 4.90$; the corresponding O-methine absorption of lactam-C is higher, at $\tau = 6.17$. Since neither pair in the methylene quartet is further split by a vicinal third proton, while the peak associated with the acetoxylated methine ($C-CH<^{OAc}_{CO-N}$) is isolated from any spin coupling, the groupings in question must be joined to a quaternary center and the five-membered ring E of aspidospermine contains the system $C-\overset{C}{\underset{C}{\dot{C}}}-CH_2-CH_2-N<$.

Mercuric acetate oxidation[7] of the alkaloid gave a mixture of enamines from which one, dehydroaspidospermine-A (VIII), was isolated as the iminium perchlorate, m.p. 256-287°, dec., (Found: C, 58.60; H, 6.74; N, 5.95. $C_{22}H_{29}O_6N_2Cl$ requires: C, 58.31; H, 6.45; N, 6.19.) with ν_{max} 1698 ($[>C=N<]^+$) and no band near 2400 cm^{-1} ($[R_3N-H]^+$). Further oxidation of the regenerated enamine with silver oxide in aqueous dioxane gave the neutral aspidospermine lactam-A (IX), m.p. 174-176°, (Found: C, 71.47; H, 7.45; N, 7.47. $C_{22}H_{28}O_3N_2$ requires C, 71.71; H, 7.66; N, 7.60.) with very strong absorption at 1625 cm^{-1}, the result of superposition of the bands due to a six-membered lactam carbonyl and the N_a-acetyl function. Deacetylaspidospermine lactam-A, prepared by acid hydrolysis and purified via the hygroscopic perchlorate,

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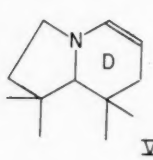
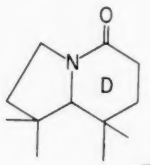
[7] Cf. N. J. Leonard and F. P. Hauck, Jr., J. Amer. Chem. Soc. 79, 5279 (1957).

m.p. 210-217°, (Found: C, 56.20; H, 6.47; N, 6.62. $C_{20}H_{27}O_6N_2Cl$ requires: C, 56.27; H, 6.38; N, 6.56.) still has ν_{max} 1621 cm^{-1}. Absence of skeletal change in the oxidations was shown by reduction of dehydroaspidospermine-A perchlorate to aspidospermine with sodium borohydride and reduction of lactam-A to N_a-ethyl-deacetylaspidospermine with lithium aluminum hydride.



VIII



IX

Dehydroaspidospermine-A bears one olefinic hydrogen at the β position (with respect to N_b) as shown by the infrared shoulder at 1651 cm^{-1} given by the free base and by the sharp peak at 1650 cm^{-1} in the spectrum of the deacetylated enamine.[8] The enamine (VIII) coupled readily with p-nitrobenzenediazonium chloride to give an intensely red dyestuff, yellow in acidic solution, as shown:

$$\text{>N-CH=CH-} \longrightarrow \text{>}\overset{+}{\text{N}}\text{=CH-CH<}_{\text{N=N-Ar}} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \text{>N-CH=C<}_{\text{N=N-Ar}},$$

which should not have been possible if the enamine had been more highly substituted at the β carbon.

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[8] If fully substituted at the β carbon, an αβ-unsaturated amine absorbs in the infrared range 1666-1673 wavenumbers; otherwise the characteristic peak is at lower frequencies (1640-1652 wavenumbers) (Ref. 7).

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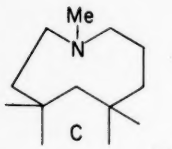
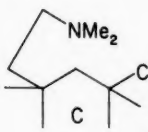
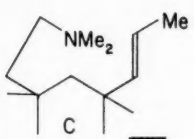
Further information as to the constitution of ring D was obtained from aspidospermine dihydromethine[2] (X), the product of Emde reduction of aspidospermine methiodide. Hofmann degradation of the dihydromethine



X



XI, R = CH=CH$_2$
XII, R = CH$_2$CH$_3$
XIII, R = CHO



XIV

methiodide[2] with potassium t-butoxide gave the olefinic base (XI), characterized as its perchlorate, m.p. 245-246° (Found: C, 59.43; H, 7.67; N, 5.72. $C_{24}H_{35}O_6N_2Cl$ requires: C, 59.44; H, 7.69; N, 5.78.). No product corresponding to an alternative course of elimination was obtained. The base (XI) shows typical vinyl infrared absorption at 910 and 995 cm^{-1}, peaks vanishing in the spectrum of the corresponding dihydrogenated derivative (XII) [perchlorate, m.p. 261°; Found: C, 59.13; H, 7.81; N, 5.74. $C_{24}H_{37}O_6N_2Cl$ requires: C, 59.19; H, 8.07; N, 5.78.]. The 60 mc/sec NMR spectrum[6] of XI shows two overlapping symmetrically spaced quartets centered at τ = 4.95 and 4.99 associated with the A and B protons of the system $CH_AH_B{=}CH_C{-}$. If the Hofmann elimination had proceeded in the other direction, giving a vinyl function substituted upon the quaternary center, the C proton should also have appeared as a quartet, with splittings which could have been deduced from those of the A and B quartets. Instead we

observed a multiplet centered near τ = 4.24 sufficiently complex to require that the C proton be coupled to four other, as in $CH_AH_B{=}CH_C{-}CH_XH_Y$.[9] The evidence for an adjacent methylene further includes the spectrum of XII [derived from the olefin (XI) by osmium tetroxide-periodate fission], with a symmetrical 1:2:1 triplet at τ = 0.17 (J = 2.9 cps) associated with the aldehydic proton resonance.[10]

The olefin (XI) was transformed by hot mineral acid into an isomer [perchlorate, m.p. 199-201° (Found: , 59.60; H, 7.78; N, 5.50. $C_{24}H_{37}O_6N_2Cl$ requires C, 59.19; H, 8.07; N, 5.78.)], which loses its vinyl absorption in the infrared and NMR but gives instead a band at 970 cm^{-1} (trans -CH=CH-), a two proton olefinic resonance multiplet at τ = 4.53 and a three proton doublet at τ = 8.32 with J = 2.6 cps (allylic C-methyl). Catalytic reduction led to a dihydro base whose identity with XII was established by infrared comparison of the bases and the two salts, and by mixed m.p. of the salts. This olefin is the double bond isomer (XIV) containing a trans-propenyl group in place of the allyl residue.

These results establish the presence of the system $>N{-}CH_2{-}CH_2{-}CH_2{-}C$ within the six-membered ring D. They exclude attachment of the C-ethyl

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[9] First order theory predicts no more than eight lines for the C resonance in $CH_AH_B{=}CH_C{-}CH_XC_2$ and only four in $CH_AH_B{=}CH_C{-}CC_3$; at least ten could be seen clearly in our spectrum and it is probable that better resolution would have disclosed twelve.

[10] The acetaldehyde -CHO resonance appears at τ = 0.28 (J = 2.85 cps).

group of I at the β carbon, as in the Witkop–Openshaw structure.[5,11,12]

The DE bicyclic system cannot be bridged so as to violate the requirements of coplanarity about N_b in the lactams and the (iminium) salt of VIII. We have no unequivocal evidence for the second quaternary center (to which is bonded the C–ethyl, in II), but its inclusion provides explanation for the isomerization (XI ⟶ XIV) proceeding no further than it does, to a disubstituted olefin, and is consistent with the behavior of the unit >CH–N_b in the NMR spectra.

In conclusion we mention that a number of our other observations, although of somewhat less direct consequence in the structural argument, are in complete agreement with the structure (II) for aspidospermine; it is with particular satisfaction that we welcome the dramatic and impressively definitive solution reached by Mills and Nyburg using the X-ray technique.

Acknowledgements – This research was supported by a grant (RG-6190) from the National Institutes of Health. Microanalyses were performed by W. Manser, E. T. H., Zurich and by Dr. S. M. Nagy, M. I. T.

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[11] The Witkop–Openshaw structure was based primarily upon Witkop's reported isolation of 3,5-diethylpyridine from zinc dust degradation of deacetylaspidospermine but it will be recalled that the product in question could not be positively identified with the synthetic sample [B. Witkop, J. Amer. Chem. Soc. 70, 3712 (1948)].

[12] H. T. Openshaw, G. F. Smith and J. R. Chalmers, XIIIth International Congress of Pure and Applied Chemistry, 1953, Abstracts, p. 223; H. T. Openshaw, and G. F. Smith, Experientia 4, 428 (1948); A. J. Everett, H. T. Openshaw and G. F. Smith, J. Chem. Soc. 1120 (1957).

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TWO NOTES ON THE LAST STAGES OF A DL RESERPINE SYNTHESIS

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Pharmaceutical and Biochemical Research Institute, Prague

(Received 5 June 1959; in revised form 18 July 1959)

WEISENBORN and Diassi[1] have already noted that a combination of the principle of Woodward's total synthesis of reserpine[2] with their reduction method[1] "would form the basis for an alternative path to reserpine". We now wish to report our results in the realization of this idea, reached independently of the suggestion of the above authors.[1]

dl Methyl O-acetyldehydroreserpate perchlorate: m.p. 208°; (Found: C, 54.18; H, 5.71; N, 5.08. $C_{25}H_{31}ClN_2O_{10}$ requires C, 54.10; H, 5.63; N, 5.05), obtained from dl methyl O-acetyl-3-oxo-2,3-secoreserpate[2] by the action of phosphorus oxychloride and then sodium perchlorate, was reduced with zinc and perchloric acid in acetone-tetrahydrofuran-water[3] and the product (m.p. 243-245°) was deacetylated by hot methanolic sodium methoxide to a mixture - separated by chromatography on alumina - of 3 parts dl methyl reserpate:[2] m.p. 240-242°; (Found: C, 67.00; H, 7.40; N, 6.80; OCH_3, 22.68.

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[1] F. L. Weisenborn and P. A. Diassi, J. Amer. Chem. Soc. 78, 2022 (1956).

[2] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, Tetrahedron 2, 1 (1958).

[3] L. Velluz, G. Muller, R. Joly, G. Nomine, J. Mathieu, A. Allais, J. Warnant, J. Valls, R. Bucourt and J. Jolly, Bull. Soc. Chim. Fr. 673 (1958).

$C_{23}H_{30}N_2O_5$ requires C, 66.64; H, 7.30; N, 6.76; OCH_3, 22.46. I.R. ($CHCl_3$) 1630, 1732, 2830, 3475 cm^{-1}) and 1 part dl methyl isoreserpate: m.p. 266-267°; (Found: C, 66.37; H, 7.18; N, 6.80; OCH_3, 22.72. $C_{23}H_{30}N_2O_5$ requires C, 66.64; H, 7.30; N, 6.76; OCH_3, 22.46. I.R. ($CHCl_3$): 1632, 1732, 2760, 2800, 2830, 3475 cm^{-1}). The former was compared with l methyl reserpate[4] by means of infra-red spectroscopy and paper chromatography; no difference was found. With acetic anhydride at 100° it gave dl methyl O-acetylreserpate: m.p. 275-276°; (Found: C, 65.92; H, 7.34; N, 6.15; OCH_3, 20.54. $C_{25}H_{32}N_2O_6$ requires C, 65.77; H, 7.07; N, 6.14; OCH_3, 20.40). The conversion of dl methyl reserpate into dl reserpine: m.p. 256-257°; (Found: C, 65.29; H, 6.59. $C_{33}H_{40}N_2O_9$ requires C, 65.11; H, 6.62) by reaction with 3,4,5-trimethoxybenzoyl chloride in pyridine[2] could largely be improved by the use of shorter reaction time (20 hr), by decreasing the excess of the acid chloride to 50 per cent only, and by using very pure pyridine (purified by way of the crystalline perchlorate): a yield of 72 per cent of the theoretical could thus be obtained.

An analogous approach was used in the deserpidine series: dl Methyl O-acetyl-3-oxo-2, 3-secodeserpidate (m.p. 215°)[5] was converted to dl methyl O-acetyldehydrodeserpidate perchlorate: m.p. 175°; (Found: C, 53.01; H, 5.43; N, 5.25. $C_{24}H_{29}ClN_2O_9.H_2O$ requires C, 53.09; H, 5.75; N, 5.16) and further to dl methyl deserpidate: m.p. 140°; (Found: C, 65.73; H, 7.10;

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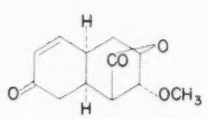
4 L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, Helv. Chim. Acta 37, 59 (1954).

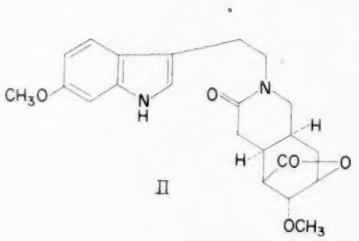
5 L. Bláha, J. Weichet, J. Žváček, S. Šmolík and B. Kakáč, Coll. Czech. Chem. Comm. 24, In press (1959).

N, 7.15; OCH_3, 15.92. $C_{22}H_{28}N_2O_4.H_2O$ requires C, 65.65; H, 7.51; N, 6.96; OCH_3, 15.42. I.R. ($CHCl_3$): 1730, 2850, 3480 cm^{-1}), which can be transformed into dl deserpidine.[5]

In another series of experiments Woodward's 2-methoxy-3-hydroxy-7-oxo-Δ^5-cis-octalin-1-carboxylic acid[2] was converted into the lactone I (m.p. 179-181°)[6], which by ozonization and further by reaction with 6-methoxy-tryptamine followed by sodium borohydride reduction gave dl 3-oxo-2,3-secoreserpic acid lactone: II, m.p. 184.5-185.5°; (Found: C, 66.48; H, 6.42; OCH_3, 15.81. $C_{22}H_{26}N_2O_5$ requires C, 66.31; H, 6.58; OCH_3, 15.58. I.R. ($CHCl_3$): 1633, 1787, 2840 cm^{-1}). This could be cyclized by phosphorus oxychloride to dl dehydroreserpic acid lactone: perchlorate, m.p. 309-311°; (Found: C, 54.51; H, 5.36; N, 5.79; OCH_3, 12.73. $C_{22}H_{25}ClN_2O_8$ requires C, 54.95; H, 5.24; N, 5.83; OCH_3, 12.90. I.R. (Nujol): 1623, 1774 cm^{-1}).



I



II

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[6] E. Adlerova, L. Blaha, M. Borovicka, I. Ernest, J. O. Jilek, B. Kakac, L. Novak, M. Rajsner and M. Protiva, Coll. Czech. Chem. Comm. 24, In press (1959).

The conversion of dehydroreserpic acid lactone into reserpic acid lactone and hence into reserpine has already been described by Muller[7] and Woodward.[2]

The authors are indebted to Dr. B. Kakáč for recording and interpretating the spectra, to Dr. K. Macek for paper chromatographic analyses and to all members of the staff of the Analytical Laboratory of our Institute for their helpful assistance.

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[7] G. Muller, Fr. Pat. 1,164.747.

Tetrahedron Letters No. 11, pp. 16-20, 1959. Pergamon Press Ltd. Printed in Great Britain.

ON THE OCCURRENCE OF HYDROGEN BONDING IN C-ALKYL- AND C-HALOGEN- FORMAZANS

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(Received 26 June 1959)

MUCH effort was directed also recently[1,4] towards the location of azo-group stretching vibration in different types of molecules, but the problem is still unsolved; the situation is somewhat complicated by the fact that the position and intensity of the band seem to be highly dependent of structural factors, and that it is often likely to be partially covered by strong, nearly located phenyl-ring vibrations; it is generally located in the range 1400-1600 cm^{-1}.

Particular interest is connected with the azo-group vibration in formazans, because there is good evidence, both from ultra-violet spectroscopic[2] and kinetic[3] data, as to the presence of a N-H...N

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[1] R. J. W. Le Fèvre et al., Aust. J. Chem. 6, 341 (1953); 10, 26 (1957); 11, 92 (1958); G. Costa, Ann. Chim. 46, 649 (1956); D. Hadzi, J. Chem. Soc. 2143 (1956); R. Mecke and E. Greinacher, Z. Elektrochem. 61, 530 (1957); K. Ueno, J. Amer. Chem. Soc. 79, 3205 (1957).

[2] I. Hausser, D. Jerchel and R. Kuhn, Ber. 82, 195, 515 (1949); 84, 651 (1951); K. H. Hausser, Naturwissenschaften 36, 313, 314 (1949); Z. Naturf. 5a, 41 (1950); R. Kuhn and H. Zahn, Ber. 84, 566 (1951); A. Foffani and A. Stuparich, Gazz. Chim. Ital. 83, 508 (1953).

[3] R. Kuhn and H. M. Weitz, Ber. 86, 1199 (1953); A. Foffani, A. Stuparich and L. Salvagnini, Gazz. Chim. Ital. 85, 175 (1955); 89, 922 (1959).

intramolecular hydrogen bond in the "red" forms of these molecules. The bond involves one nitrogen atom of the azo-group, and its occurrence is likely therefore to cause a noticeable frequency lowering of the azo-band, giving for this very fact an additional criterion for its location.

In the recent infra-red work on formazans[4] there was not taken advantage of this situation, because only triphenyl-derivatives were examined, and these are known to exist almost completely in their red form in all physical conditions, except under ultra-violet irradiation.

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We have extended the infra-red study to C-hydrogen-N,N"-diphenylformazan and to the corresponding C-chloro, C-iodo, C-methyl- and C-ethyl-derivatives, which are particularly suitable for the present purpose, since the first three compounds appeared, from previous evidence,[2] to be stable only in the "yellow" form, while the last two give rise to equilibria between the two forms in convenient media, and the equilibrium position is quite sensitive to ultra-violet irradiation.

For the recording of the spectra two Perkin Elmer instruments were used, a double beam Model 21 and a single-beam double-pass Model 112, with NaCl and CaF_2 and, for the N-H stretching region, also with LiF optics. The compounds were examined in a series of polar and non-polar solvents of widely different character, as well as in the solid state (as KBr pellets and, where feasible, also as Nujol or hexachlorobutadiene mulls).

The analysis of the spectra (for details see ref. 5) gives results

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[4] R. J. W. Le Fèvre et al., Aust. J. Chem. 9, 151 (1956); see also 10, 32 (1957).

[5] A paper by the same authors, to be presented before the Meeting of European Molecular Spectroscopists, Bologna, Italy, 7-12 Sept. (1959).

of particular interest in connection with the present discussion in the N-H stretching region and in the 1400-1600 cm^{-1} range.

In the N-H stretching region there is observed that, in the cases where previous evidence[2] indicated the system as being prevailingly in its yellow form, a well developed band of mean intensity is present indeed in the range 3300-3350 cm^{-1} in solution, while strongly shifted (by about 100 cm^{-1}) to lower frequencies on going to the solid state. This is the case of the C-hydrogen-, C-chloro- and C-iodo-derivatives in all physical conditions, and of the corresponding C-methyl- and C-ethyl- as yellow solids and as benzene solutions of these solid forms when examined just after dissolution. No band is observed in this region in the red forms.

We have extended the study to a wide range of solvents, observing typical solvent effects: (a) in such non-polar solvents as CCl_4, C_2Cl_4 or C_6H_6 the band is sharp and has its highest frequency value, but in the case of the C-methyl- and C-ethyl-compounds it disappears more or less rapidly with time; (b) in such polar media as acetonitrile, pyridine, dioxane or ethyl ether the band, fairly stable with time, is much broader and at much lower frequencies, often comparable to those observed in the solids. Some actual approximate values for the typical case of the C-methyl-derivative are: CCl_4 and C_2Cl_4 3357; CH_2Cl_2 3352; CS_2 3347; C_6H_6 3345; CH_3CN and C_6H_5CN 3305; dioxane 3287; ethyl ether 3284; pyridine 3225 cm^{-1}.

Such a behaviour is readily explained on admitting the red forms of our molecules actually being intramolecularly bonded (with the yellow-red equilibrium position being reached more or less rapidly according to the type and purity of the non-polar solvent), and the yellow forms being partially linked through solute-solvent interaction in polar solutes and

in the solid state. In this respect, it is remarkable that the yellow form is stable not only in hydroxylic solvents, as previously verified,[2] but also in typical proton-accepting media such as ether and dioxane, and in solvents such as nitriles which are known[6] to act mainly through dipole-dipole associations. In the red forms the N-H stretching vibration, strongly lowered in frequency, has been presumably covered by the C-H stretching band around 3000 cm^{-1} or drastically weakened.

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Going now to the region (1400-1600 cm^{-1}) where the -N=N- stretching mode should presumably be observed, the examination of the spectra (see ref. 5) shows that only one intense band is present indeed which cannot reasonably be interpreted as a ring vibration; its dependence on structural factors and on the solvent is in quite a good agreement with its being assigned to such a stretching mode. The band, lying in the somewhat restricted range 1530-1590 cm^{-1}, is fairly stable in position, in all conditions, in the C-hydrogen-, C-chloro- and C-iodo-derivatives; correspondingly it shifts to lower frequencies by about 23 cm^{-1} both in the C-methyl- and the C-ethyl-derivative on going from the yellow to the red, hydrogen-bridged, form. The positions in C_2Cl_4 are as follows: C-hydrogen- 1547; C-chloro- 1552; C-iodo- 1550; C-methyl-(yellow) 1581; C-methyl-(red) 1558; C-ethyl-(yellow) 1576; C-ethyl-(red) 1553 cm^{-1}.

The parallelism with the behaviour of the N-H stretching vibration is even more remarkable on looking to the variations of our band with time for the C-alkyl-derivatives: in the conditions where, as mentioned before, the

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[6] A. Foffani, C. Pecile and F. Pietra, Nuovo Cim. In press (1959); L. J. Bellamy, R. L. Williams and H. E. Hallm, Trans. Faraday Soc. 54, 1120 (1958); 55, 14 (1959); E. L. Zhukova, Optika i Spek. 4, 750 (1958).

N-H stretching is disappearing, the intensity of the peak at 1581, respectively 1576 cm^{-1} is decreasing, while correspondingly that of the low-frequency one, initially absent, is increasing.

The possibility of the assignment of the band to a N-H bending mode seems to be ruled out, taking also into account the fact that, apart from the relatively small frequency shift, the intensity of the band is almost unaffected on passing from the yellow to the red form; this should be difficult to understand for a bending mode of the N-H bond, which is directly involved in the N-H...N hydrogen bond. It is however to be pointed out that our assignment, although in general agreement with the present experimental evidence, is only tentative and clearly requires further confirmation.

Work is in progress on the effect of ligands capable of giving intermolecular N-H...N bonds with the -N=N-, respectively with the N-H group of the formazan molecule, in competition with the intramolecular hydrogen bond active in the red forms; we are also planning the study of formazans deuterated and alkylated in their N-H group.

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ON THE ASSIGNMENT OF AZOTHIO-GROUP STRETCHING VIBRATIONS IN AZOTHIOBENZENES

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(Received 26 June 1959)

RECENTLY one of us (G.L.) described the preparation of azothio-benzenes, the sulphur-analogues of azoxybenzenes, by the action of sodium metal in boiling toluene solution on the corresponding thio-nylanilines;[1a] good evidence was obtained as to the proposed structure of the reaction products from their chemical reactivity[1a] and ultra-violet spectra.[1b]

From our knowledge,[2] there does not appear to be any specific infra-red study on organic molecules containing N-S bonds, owing perhaps also to the somewhat uncommon occurrence of such bonds. We give here briefly some relevant infra-red data pertaining mainly to the -NNS- part of our molecules, while a more detailed report on the infra-red work is being prepared for

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[1a] G. Leandri and P. Rebora, Experientia 13, 71 (1957); Gazz. Chim. Ital. 87, 503 (1957); b G. Leandri and A. Mangini, Boll. Sci. Fac. Chim. Ind. Bologna 15, 51 (1957).

[2] For reviews see L. J. Bellamy, The Infra-red Spectra of Complex Molecules, Chap.22. Methuen, London (1958); L.J. Bellamy, in Organic Sulphur Compounds, (Edited by N. Kharasch). Pergamon Press, New York (1959); J. Lecomte, in Handbuch der Physik, Band 26, Licht un Materie II, Chap.D.XX. Springer, Berlin (1958).

publication elsewhere.[3] The molecules examined are azothiobenzene $C_6H_5-N=\underset{S}{N}-C_6H_5$ and its -Cl, -Br, $-CH_3$, $-OCH_3$ and $-C_6H_5$ p-disubstituted derivatives. The spectra were recorded on a Perkin-Elmer Model 21 double-beam instrument with NaCl optics, for solutions in CCl_4, C_2Cl_4 and CS_2 and partly in the solid (as KBr pellets) and liquid state.

The general features of the spectra, as refers to the ring vibrations and to those pertaining to the substituent group, are as a whole in excellent agreement, both in position and intensity, with the recent detailed work by Maier and Englert[4] on azoxybenzenes, with a few noticeable exceptions to be discussed later;[3] such a behaviour strongly supports again the structure proposed for our molecules as azoxy-similar.

Referring now to the azothic-group symmetrical and asymmetrical stretching vibrations, their location may be foreseen, as a very rough approximation, on considering that: (a) the azoxy-group asymmetrical stretching vibration falls in the range 1450-1480 cm^{-1},[4] indicating that it partakes mainly the character of an -N=N- stretching mode;[5] the same

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[3] A paper by the same authors, to be presented before the Meeting of European Molecular Spectroscopists, Bologna, Italy, 7-12 Sept. (1959).

[4] W. Maier and G. Englert, Z. Elektrochem. 62, 1020 (1958); see also B. Witkop and H. M. Kissman, J. Amer. Chem. Soc. 75, 1975 (1953); J. Jander and R. N. Haszeldine, J. Chem. Soc. 919 (1954).

[5] R. J. W. LeFèvre et al., Aust. J. Chem. 6, 341 (1953); 9, 151 (1956); 10, 26 (1957); 11, 92 (1958); G. Costa, Ann. Chim. 46, 649 (1956); D. Hadzi, J. Chem. Soc. 2143 (1956); R. Mecke and E. Greinacher, Z. Elektrochem 61, 530 (1957); K. Ueno, J. Amer. Chem. Soc. 79, 3205 (1957); as to the effect of hydrogen bonding on -N=N- stretching in formazans see A. Foffani, C. Pecile and S. Ghersetti, Tetrahedron Letters No. 11, 16, (1959).

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should essentially be valid for the corresponding azothio- stretching mode, to be expected falling therefore around the same region; (b) also the azoxy-symmetrical stretching is found,[4] fairly unsensitive to structural effects, in the sharp range 1315-1335 cm^{-1}, namely in a position not far from that (1200-1300 cm^{-1}) normally observed for the stretching mode of N-O bond in N-oxides;[6] by comparing now for example the mean location[2] of C=O and C=S stretching vibrations, from the mean ratio $\nu_{C=O}/\nu_{C=S} = 1.1+1.6$ it is reasonable, by simple mass effect, to expect finding the azothio-group symmetrical stretching mode in the region 900-1100 cm^{-1}.

Looking now to the spectra, it is easily observed (for details see ref. 3) that indeed in the suspected regions, and only there, two strong bands are present which cannot reasonably be identified as ring- or substituent-group-vibrations. Their approximate position is as follows: azothiobenzene (AT) 1070, 1448; p,p'-di-chloro-AT 1063, 1459; p,p'-dibromo-AT 1058, 1458; p,p'-dimethyl-AT 1062, 1448; p,p'-dimethoxy-AT 1068, 1463; p,p'-diphenyl-AT 1070, 1448 cm^{-1}.

The high intensity of the bands and the great similarity of their form from compound to compound supports well their belonging to fundamental stretching modes of the central part of the molecules; the experimental ranges are therefore 1065 ± 6 cm^{-1} for the asymmetrical vibration. We are careful however to point out that in the lack of further information,

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[6] G. Costa et al., Gazz. Chim. Ital. 85, 1085 (1955); Z. Phys. Chem. Neue Folge 4, 24 (1955); 7, 123 (1956); R. H. Wiley and S. C. Slaymaker, J. Amer. Chem. Soc. 79, 2233 (1957); A. R. Katritzky et al., J. Chem. Soc. 2182, 2192, 2195 (1958); for quinoline N-oxides see A. Foffani, G. Favaro and A. Risaliti, Unpublished results.

particularly of measurements in polarized light on oriented samples,[4] some degree of uncertainty surely remains in our present tentative assignments; this is especially true, as discussed,[3] for the asymmetrical mode, which falls near to a ring vibration and in some cases cannot unequivocally be distinguished from it.

16–SUBSTITUTED STEROIDS

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Division of Chemical Research, G. D. Searle & Co., Skokie, Ill.

Abstract—The reactions of 3β-acetoxy-5,16-pregnadien-20-one with cyanide ion and with certain active methylene compounds are described. Subsequent transformations of the initial products to give various 16-substituted pregnenolones and progesterones are shown.

1959

TERPENOIDS—VI

A NOVEL UNAMBIGUOUS SYNTHESIS OF DL–AR–TURMERONE

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Department of Chemistry, Panjab University, Hoshiarpur, India

Abstract—A new synthesis of DL-ar-Turmerone starting from DL-curcumone is described.

The aromatic ketone DL-ar-Turmerone (I) occurs with Turmerone (II) a monocyclic sesquiterpene ketone, as chief component of the essential oil from the rhizomes of *Curcuma longa* Linn.

STEROIDS—CXX SYNTHESIS OF HALOGENATED STEROID HORMONES

NEW ROUTES TO 6α-FLUOROTESTOSTERONE AND THE 6α- AND 6β-FLUORO ANALOGS OF PROGESTERONE. THE SYNTHESIS OF 6α- AND 6β-FLUORO REICHSTEIN'S COMPOUND "S" AND 6α- AND 6β-FLUORODESOXYCORTICOSTERONE ACETATE

A. BOWERS, L. CUÉLLAR IBÁÑEZ and H. J. RINGOLD
Research Laboratories, Syntex, S.A., Mexico City

Abstract—The conformational and electronic factors involved in the fission of steroid 5α,6α-epoxides with boron trifluoride-etherate are discussed with particular reference to C-3-keto-5α,6α-epoxides and their cycloethylene-dioxy derivatives.

These considerations led to the development of a new synthesis of 6-fluoro-Δ^4-3-ketones from the corresponding Δ^4-3-ketones via the boron trifluoride-etherate cleavage of their derived cycloethylene-ketal-5α,6α-epoxides.

Application of this method led to the synthesis of 6α-fluorotestosterone and the 6α and 6β-fluoro analogs of progesterone desoxycorticosterone acetate and Reichstein's Compound "S" diacetate. The latter compound and its Δ^1-analog are valuable precursors for the 6-fluoro cortical hormones.

STEROIDS—CXXI SYNTHESIS OF HALOGENATED STEROID HORMONES

6α-FLUORO CORTICAL HORMONES A NEW CLASS OF POWERFUL CORTICOIDS

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Abstract—Incubation of 6α-fluoro-Reichstein's Compound "S" (I) and its Δ^1-analog (IV) with bovine adrenals followed by acetylation led to 6α-fluorohydrocortisone acetate (II) and 6α-fluoroprednisolone acetate (III) respectively. Selenium dioxide oxidation of II also afforded III. Chromium trioxide oxidation of II and III gave 6α-fluorocortisone acetate (VIIa) and 6α-fluoroprednisone acetate (VIIIa) respectively. An alternate, all-chemical synthesis of 6α-fluorocortisone acetate (VIIa) from cortisone acetate (V) is described.

Dehydration of 6α-fluorohydrocortisone acetate gave 6α-fluoro-$\Delta^{9(11)}$-dehydro Compound "S" (XIV). Formation of the corresponding 9β,11β-epoxide (XV) and reaction with hydrogen fluoride then gave 6α,9α-difluorohydrocortisone acetate (XVI) which afforded the prednisolone analog (XVII) upon oxidation with selenium dioxide.

POLYMORPHISM IN SUBSTITUTED BARBITURIC ACIDS

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Wellington, New Zealand

Abstract—Of twenty substituted barbituric and thiobarbituric acids studied, nine have been found to exist in polymorphic forms. These are barbital, butethal, amobarbital, pentobarbital, thiopental, phenobarbital, aprobarbital, nostal and kemithal. The different modifications have been studied by X-ray diffraction and infra-red spectrophotometry, and the transition temperature ranges have been determined. The forms found are divided into two groups on the basis of their infra-red spectra. The tautomeric form of the compounds in the solid state is discussed briefly.

STUDIES IN SESQUITERPENES—XVI

ZERUMBONE, A MONOCYCLIC SESQUITERPENE KETONE

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Bangalore, India

Abstract—The structure, previously assigned to zerumbone, has been found to be untenable. The ketone has been shown to be monocyclic containing three ethylenic linkages, and has been further correlated with humulene. Results from ozonolysis, and base-catalysed cleavage allow the compound to be formulated as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one.

1959

Tetrahedron Letters, No.12, pp. 1-5, 1959. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF CASTORAMINE

Z. Valenta and A. Khaleque

Department of Chemistry, University of New Brunswick,

Fredericton, N.B.

1959

(Received 14 July 1959)

THE scent glands of the beaver, known commercially under the name castoreum, contain a veritable treasure of organic substances, presumed to be derived mainly from barks and buds of trees, the beaver's principal food. One of the interesting castoreum constituents isolated and investigated by Lederer[1,2] is the base castoramine, $C_{15}H_{23}O_2N$. According to Lederer, castoramine is a strong base which is relatively unstable to light and oxygen. It can be purified by recrystallization of the corresponding sulphate, m.p. 212-216°, from which the free base can be liberated in crystalline form, m.p. 65-66°.[2] The French author further reported that castoramine contains no methoxyl or N-methyl groups and shows no active hydrogen in the Zerewitinoff determination. The base did not react with 2, 4-dinitrophenylhydrazine and was found to be resistant to acid or alkaline hydrolysis and to a catalytic hydrogenation with palladium on charcoal.

We became interested in castoramine since it appeared that it should

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[1] E. Lederer, Perfumery Essent. Oil Rec. 40, 353 (1949).

[2] E. Lederer, Bull. Soc. Chem. Biol. 25, 1381 (1943).

be either a sesquiterpene base or a compound biologically formed by a multiple acetate and/or propionate condensation. The extraction of the basic material from the air-dried glands of the Canadian beaver followed by a distillation, yielded an oily fraction (125-135°/0.08 mm Hg) which according to its infrared spectrum was almost pure castoramine (yield = 0.4 per cent of partially dried glands). The analysis of the crystalline sulphate and the sublimed free base confirmed Lederer's $C_{15}H_{23}O_2N$ formula. Castoramine was found to contain one C-methyl group (50 per cent), no methoxyl and no N-alkyl. In contrast to Lederer's report, however, our analytical results indicated one active hydrogen in the molecule. The infrared spectrum of castoramine showed a band at 3250 cm^{-1} ($CHCl_3$) and acetylation of the base with acetic anhydride-pyridine yielded an oily basic acetate (Found: C, 70.14; H, 8.49; O, 16.32; N, 4.62. $C_{17}H_{25}O_3N$ requires: C, 70.16; H, 8.66; O, 16.49; N, 4.82) (I.R. max. = 1725 cm^{-1} in $CHCl_3$), showing the presence of a hydroxyl group in castoramine.

The nature of the second oxygen became clear when it was realized that castoramine contains a furan ring. While the ultraviolet spectrum of the base showed only end-absorption, the presence of an aromatic system was indicated by the uptake of 2-3 moles of hydrogen on reduction of the sulphate with an active platinum catalyst and by sharp I.R. peaks at 1505 and 872 cm^{-1}. The NMR spectrum of castoramine[3] with peaks at -104 counts/sec (double intensity) and -70 counts/sec (single intensity) quite clearly

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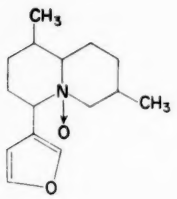
[3] The spectrum was determined with a 60 mc/sec instrument in chloroform solution. The values have been converted to c.p.s. relative to water at 40 mc/sec for easier reference with the literature values (See ref. 4). We thank Dr. R. R. Frazer, University Ottawa, for doing this determination for us.

established the presence of a β-monosubstituted furan ring[4]. A C-methyl peak at +162 counts/sec (triple intensity) confirmed our analytical value mentioned earlier.

At this point it became attractive to speculate that castoramine is in fact a sesquiterpene containing one oxygen ring and one or more likely two nitrogen rings. Now such a compound has already been found in Nature by two Japanese groups.[5,6] In an excellent degradative study, they found that the alkaloid nupharidine, obtained from the water-lily Nupher japonicum was the N-oxide (I). Since the Canadian beaver is known to feed on stems and roots of water-plants, a relationship between the two bases became very likely.



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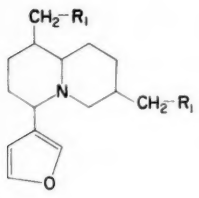

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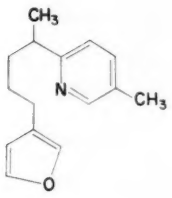

III

The reaction of castoramine with phosphorus oxychloride gave a

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[4] E. J. Corey, G. Slomp, S. Dev, S. Tobinaga and E. R. Glazier, J. Amer. Chem. Soc. 80, 1204 (1958).

[5] M. Kotake, S. Kusumoto and T. Ohara, Liebigs Ann. 606, 148 (1957).

[6] Y. Arata and T. Ohashi, J. Pharm. Soc. Japan 77, 236 (1957).

chloro-compound $C_{15}H_{22}ONCl$, m.p. 68°, which could also be obtained by a treatment of the base with tosyl chloride in pyridine. Reduction of the chloro-compound in boiling glacial acetic acid with zinc dust in the presence of sodium iodide gave an oily base which could be purified through its crystalline hydrochloride, m.p. 215-220°. This base was found to be identical by infrared spectra with desoxynupharidine (II) ($R_1 = R_2 = H$) obtained by the Japanese workers by the reduction of (I)[7,8].

It follows that the structure of castoramine is (II) ($R_1 = H$, $R_2 = OH$) or (II) ($R_1 = OH$, $R_2 = H$). Selenium dehydrogenation of castoramine gave an oily base, which was purified through the crystalline picrate, m.p. 69-71° (!)and sublimed for analysis. (Found: C, 78.59; H, 8.32; O, 7.29; N, 6.32. $C_{15}H_{19}NO$ requires: C, 78.67; H, 8.36; O, 6.99; N, 6.12). Its ultraviolet spectrum (λ_{max} = 268 mμ, ε = 7400 with inflections at 262 and 275 mμ) indicated a disubstituted pyridine derivative. We believe that the dehydrogenation product is in fact (III), also obtained by the Japanese workers from desoxynupharidine[5]. For this reason, we prefer structure (II) ($R_1 = H$, $R_2 = OH$) for castoramine.

Two further observations deserve comment. Unlike simple furans, castoramine is very stable to aqueous acid. Prolonged boiling with sulphuric acid in ethanol destroyed only a small part of the material. Obviously, the charged nitrogen makes a further attack of a positive ion

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[7] S. Kusumoto, J. Japan Chem. Soc. 78, 488 (1956).

[8] We thank Dr. Kusomoto, Osaka University, Japan, for making this article available to us. We are also grateful to him for supplying us with a generous sample of desoxynupharidine hydrochloride.

very difficult. Secondly, castoramine acetate (see above) shows an I.R. maximum at 1725 cm^{-1} ($CHCl_3$), while the corresponding hydrochloride has the acetate peak in the usual position (1740 cm^{-1} in $CHCl_3$). It appears that the tertiary nitrogen of the free base can interact with the acetate carbonyl group (1,6 relationship).

Additional reactions of castoramine together with stereochemical considerations will be published at a later date. We are at the present time investigating the alkaloid content of New Brunswick water-lilies.

One of us (A.K.) gratefully acknowledges the financial support of the Colombo Plan Administration of Canada.

1959

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THE RELATIVE CONFIGURATION AT $C_{(22)}$ AND $C_{(23)}$ IN VERATRAMINE AND JERVINE

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Czechoslovak Academy of Science, Prague

(Received 15 July 1959)

CONSIDERATION of the stereochemistry of the piperidine moiety of veratramine (I)[1] shows that the side chain on $C_{(22)}$ must be the conformation determining substituent and hence equatorial. Therefore, if the hydroxyl group on $C_{(23)}$ is configurationally cis to this substituent, the hydroxyl will be largely in the axial conformation; on the other hand, if these two groups are trans, the hydroxyl will be equatorial. If, therefore, the axial or equatorial nature of the hydroxyl group were known, the relative configuration at the centres $C_{(22)}$ and $C_{(23)}$ in veratramine could be established.

We have recently suggested that the axial or equatorial nature of the hydroxyl group in 3-hydroxypiperidine derivatives may readily be deduced from the hydroxyl stretching frequencies in the 3μ region:[2] only the axial

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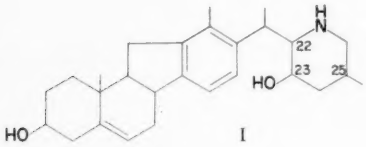
[1] Ch. Tamm and O. Wintersteiner, J.Amer. Chem. Soc. 74, 3842 (1952).

[2] J. Sicher and M. Tichý, Coll. Czech. Chem. Comm. 22, 2081 (1958).

hydroxyl can engage in hydrogen bonding with the ring nitrogen atom. The spectrum of a 3-hydroxypiperidine derivative containing a hydroxyl group in the axial conformation will therefore exhibit two concentration independent hydroxyl bands (free and associated) in the 3μ region, while that of a derivative with an equatorial hydroxyl group will show only a single hydroxyl band (free).

1959



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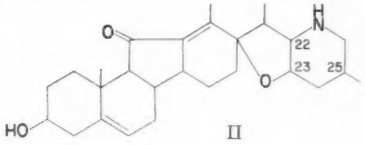

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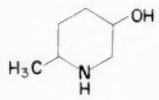

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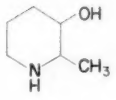

IV

cis, m.p. 48·5 – 49·5°
ν(OH)$_{free}$ 3625 cm^{-1}
ν(OH)$_{assoc.}$ 3532 cm^{-1}
trans, m.p. 97 – 97·5°
ν(OH)$_{free}$ 3624 cm^{-1}

cis, m.p. 94·5 – 95·5°
ν(OH)$_{free}$ 3632 cm^{-1}
ν(OH)$_{assoc.}$ 3526 cm^{-1}
trans, m.p. 138·5 – 139·5°
ν(OH)$_{free}$ 3632 cm^{-1}

In accordance with this rule we have found that of the two pairs of pipecolinol derivatives, III and IV, prepared as models for a semi-quantitative study to be reported on a subsequent occasion, the cis-isomers exhibit two hydroxyl bands in the 3μ region, the trans-isomers only a single

hydroxyl band.[3] On the basis of these considerations we have already been able to determine the relative configuration of the propyl and hydroxyl group in the alkaloid φ-conhydrine (trans-2-propyl-5-hydroxypiperidine).

We have now found that the spectrum of veratramine contains a single OH band (3619 cm^{-1}). This proves that the hydroxyl group on $C_{(22)}$ is equatorial and therefore that the substituents on $C_{(22)}$ and $C_{(23)}$ in veratramine (I) are trans to each other. It has been shown by Wintersteiner and Moore[4] that the configurations at $C_{(22)}$ and $C_{(23)}$ in jervine (II) are the same as those in veratramine. Our results therefore also establish the relative configurations at $C_{(22)}$ and $C_{(23)}$ in jervine and hence show that the tetrahydrofuran ring in jervine is annelated to the piperidine ring in a trans fashion. The position of the methyl group on $C_{(25)}$ in both alkaloids relative to the hydroxyl group remains undecided.

We are greatly indebted to Dr. O. Wintersteiner (Squibb Institute for Medical Research, New Brunswick, N.J.) for a sample of veratramine and for very valuable comment on the relation between veratramine and jervine.

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[3] The spectra were measured by Dr. M. Horák of this Institute. For the technique used see J. Sicher, M. Horák and M. Tichý, Coll. Czech. Chem. Comm. 24, 950 (1959).

[4] O. Wintersteiner and M. Moore, J. Amer. Chem. Soc. 78, 6193 (1956).

Tetrahedron Letters, No. 12, pp. 9-11, 1959. Pergamon Press Ltd. Printed in Great Britain.

STUDIES IN PURINE CHEMISTRY. VI. A CONVENIENT ONE-STEP SYNTHESIS OF HYPOXANTHINE[1,2]

Edward C. Taylor and C. C. Cheng

Frick Chemical Laboratory, Princeton University, Princeton, N. J.

1959

(Received 16 July 1959)

EXISTING methods for the preparation of hypoxanthine fall into three categories: (i) cyclization of 4-hydroxy-5, 6-diaminopyrimidine with one-carbon reagents such as formamide and/or formic acid[3,4] or ethyl orthoformate,[5] and treatment of 4-chloro-5, 6-diaminopyrimidine with formamide,[6] (ii) cyclization of 4-aminoimidazole-5-carboxamide with similar one-carbon reagents,[7,8] and base-catalysed cyclization of

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[1] For the previous paper in this series, see E. C. Taylor and C. C. Cheng, J. Org. Chem. In press.

[2] This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

[3] G. B. Elion, E. Burgi and G. H. Hitchings, J. Amer.Chem.Soc. 74, 411 (1952).

[4] H. Getler, P. M. Roll, J.F. Tinker and G. B. Brown, J. Biol. Chem. 178, 259 (1949).

[5] E. C. Taylor and C. C. Cheng, J. Org. Chem. In press.

[6] R.K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, J. Amer. Chem. Soc. 75, 263 (1953).

[7] E. Shaw, J. Biol. Chem. 185, 439 (1950).

4-formylaminoimidazole-5-carboxamide,[7] and (iii) modifications of preformed purines, such as desulfurization of 2-mercaptohypoxanthine,[3,9] hydrolysis of adenine,[4,10] 6-cyanopurine,[11] 6-chloropurine[12] and 6-alkylmercaptopurines,[13] and treatment of xanthine with formamide.[14,15] A recently described synthesis of hypoxanthine by the reaction of ethyl orthoformate with aminomalonamidamidine dihydrochloride falls into category (ii), since it has been shown that 4-ethoxymethyleneaminoimidazole-5-carboxamide is initially formed.[8]

We have now found that hypoxanthine may conveniently be prepared in 75 per cent yield in a single step from the commercially available aliphatic intermediate, ethyl acetamidocyanoacetate, by heating with a mixture of ethyl orthoformate, ammonium acetate and alcoholic ammonia.[16] The rationale

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[8] E. C. Taylor, E. Richter and J. E. Loeffler, J.Amer. Chem. Soc. In press.

[9] W. Traube, Liebigs Ann. 331, 64 (1904).

[10] P. Reichard, J. Biol. Chem. 179, 773 (1949).

[11] L. B. MacKay and G. H. Hitchings, J. Amer. Chem. Soc. 78, 3511 (1956).

[12] A. Bendich, P. J. Russell, Jr. and J. J. Fox, J. Amer. Chem. Soc. 76, 6073 (1954).

[13] T. P. Johnston, L. B. Holum and J. A. Montgomery, J. Amer. Chem. Soc. 80, 6265 (1958).

[14] Ger. Pat., 806,670; Chem. Abstr. 46, 1035 (1952).

[15] Ger. Pat., 804,210; Chem. Abstr. 45, 8037 (1951).

[16] Ethyl acetamidocyanoacetate has recently been utilized (D. S. Acker and J. E. Castle, J. Org. Chem. 23, 2010 (1958) as an intermediate for a convenient two-step synthesis of various 2-substituted hypoxanthines, but hypoxanthine itself is apparently not available by this method.

for this synthesis rests upon a recent discovery in this laboratory[17] that formamidine acetate may be prepared in high yield by heating ethyl orthoformate with ammonium acetate and alcoholic ammonia. Ethyl acetamidocyanoacetate would be converted to its amide and its acetyl grouping removed under the reactions conditions employed, and it is known[18] that aminocyanoacetamide reacts with formamidine to give 4-aminoimidazole-5-carboxamide. The conversion of the latter compound to hypoxanthine with ethyl orthoformate has already been demonstrated.[8]

1959

Experimental

Hypoxanthine. A mixture of 2.5 g of ethyl acetamidocyanoacetate, 2.5 g of ammonium acetate, 10 ml of ethyl orthoformate and 15 ml of a 20% ethanolic ammonia solution was heated in a steel bomb at 180° for 8 hr. The dark brown residue was filtered from the reaction mixture and recrystallized from boiling water (with the use of charcoal) to give 1.5 g (75%) of a light tan solid, m.p. $>360^{\circ}$. The product was identified as pure hypoxanthine by comparison with an authentic sample by paper chromatography and by examination of infrared and ultraviolet absorption spectra.

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[17] E. C. Taylor and W. E. Ehrhart, To be published.

[18] A. H. Cook, I. Heilbron and E. Smith, J.Chem.Soc. 1440 (1949).

Tetrahedron Letters, No. 12, pp. 12-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

REARRANGEMENT OF N-SUBSTITUTED 1-THIOCARBAMYLAZETIDINES INTO DERIVATIVES OF 2-IMINO-3,4,5,6-TETRAHYDRO-1,3-THIAZINE

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(Received 20 July 1959)

THE rearrangement of N-substituted 1-thiocarbamylaziridines into derivatives of 2-amino-2-thiazoline is well known.[1,2,3] It was of interest to prepare some hitherto unknown related compounds with four-membered rings and to investigate their behaviour under conditions applied for rearrangement of three-membered rings.

The N-substituted (mainly aryl) 1-thiocarbamylazetidines (I) were prepared from azetidine[4] and the corresponding isothiocyanates. Thus the following substances (I) were prepared: R: phenyl-, m.p. 112° (lit.[4] gives m.p. 110°), R: p-tolyl-, m.p. 144-5°, R: 2',4'-dimethylphenyl-, m.p. 167°, R: p-ethoxyphenyl-, m.p. 120°, R: m-chlorophenyl-, m.p. 112° and R: p-chlorophenyl-, m.p. 146-7°.

These compounds, when heated for 15 min with excess conc. hydrochloric

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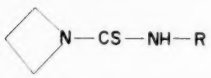
[1] S. Gabriel and R. Stelzner, Ber. 28, 2929 (1895).

[2] A. S. Deutsch and P. E. Fanta, J. Org. Chem. 21, 892 (1956).

[3] M. Tišler, Arch. Pharm. 291/63, 457 (1958).

[4] C. C. Howard and W. Marckwald, Ber. 32, 2031 (1899).

acid, were almost quantitatively transformed into derivatives of 2-imino-3,4,5,6-tetrahydro-1,3-thiazine (II).



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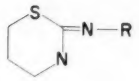


II

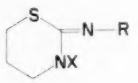
1959

It is well known that the relatively unstable azetidine and its derivatives readily open the ring when treated with acids giving rise to derivatives of n-propylamines or γ-hydroxypropylamines, the last reaction taking place preferentially in dilute acid solution.

Through rearrangement the following compounds (II) were obtained: R: phenyl, m.p. 127°, R: p-tolyl-, m.p. 140°, R: p-ethoxyphenyl-, m.p. 132°, R: m-chlorophenyl-, m.p. 150°, and R: p-chlorophenyl-, m.p. 156-7°. However, the synthesis of these compounds can be performed in a much simpler way, e.g. the corresponding isothiocyanates were condensed in alcoholic solution with 3-aminopropanol-(1) and the resulting condensation products, without being isolated, were thereafter cyclized with hot conc. hydrochloric acid. Compounds, obtained by this procedure, showed no depression in m.p. with those obtained through rearrangement. Accordingly, besides the above compounds the following new ones were prepared: II, R: o-tolyl-, m.p. 121°, R: m-tolyl-, m.p. 90-1°, R: p-methoxyphenyl-, m.p. 144°, R: o-methoxyphenyl-, m.p. 127° and R: cyclohexyl-, m.p. 113°.

Monosubstituted 2-imino-3,4,5,6-tetrahydro-1,3-thiazines are capable

to exist in two forms, e.g. in the imino form as III (X: H) or in the amino form as IV (X: H).



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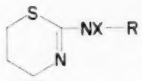

IV

With closely related substances some authors formulated them in the imine form[5,6] but many of them prefer the amino form.[7,8,9,10] The formulation as III is obvious if X in the imino group in the ring is other than hydrogen as in the case of 3-alkyl- or 3-aryl-analogues.[11,12] On the basis of infra-red spectra of II (R: phenyl-), its N-methyl derivative (III, X: CH_3-) (b.p. 175-180°/12 mm) and its N-phenyl derivative (III, X: C_6H_5-)[11,13] the

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[5] S. Gabriel and T. Posner, Ber. 28, 1029 (1895).

[6] S. Gabriel and W. E. Lauer, Ber. 23, 87 (1890).

[7] N. Ghosh, J. Indian Chem. Soc. 11, 23 (1934).

[8] A. Luchmann, Ber. 29, 1420 (1896).

[9] G.W. Raiziss, L. W. Clemence and M. Freifelder, J. Amer. Chem. Soc. 63, 2739 (1941).

[10] M. Fränkel, Ber. 30, 2497 (1897).

[11] F. B. Dains, R. Q. Brewster, J. S. Blair and W. C. Thompson, J. Amer. Chem. Soc. 44, 2637 (1922).

[12] G. Noah, Ber. 23, 2195 (1890).

[13] F. Foerster, Ber. 21, 1857 (1888).

structure III seems the most probable also for the monosubstituted compounds (III, X: H).

All m.p. were determined with Kofler's heating microscope and all analyses were in agreement with data, calculated for the above mentioned compounds. A more detailed description of these and related experiments will be reported elsewhere. The author thanks Prof. D. Hadži for measurement of the infra-red spectra.

1959

Tetrahedron Letters No. 12, pp. 16-17, 1959. Pergamon Press Ltd. Printed in Great Britain.

NITROFERROCENE

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(Received 17 July 1959)

NUMEROUS attempts to prepare nitroferrocene have been reported to be unsuccessful, both by direct nitration of ferrocene,[1,2,3,4] and from nitrocyclopentadiene.[1] This compound has now been prepared in low yield by treatment of lithioferrocene[5,6,7] with n-propyl nitrate at -70°. The compound forms deep purple needles; a sample twice-sublimed and recrystallized from cyclohexane had m.p. 130°. (Found: C, 52.06; H, 3.95; N, 5.95; Fe, 24.20. $C_{10}H_9$ Fe NO_2 requires C, 51.99; H, 3.93; N, 6.06; Fe, 24.18%). Nitroferrocene is stable in air, but decomposes slowly above 190°.

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1 M. Rosenblum, Ph.D. Thesis, Harvard University, August, 1953.

2 P. L. Pauson, Quart. Rev. 9, 391 (1955).

3 E. O. Fischer and H. P. Fritz, Advanc. Inorg. Chem. Radiochem. 1, 55 (1959).

4 P. W. K. Woo and K. L. Rinehart, Jr., Unpublished results.

5 R. A. Benkeser, D. Goggin and G. Schroll, J. Amer. Chem. Soc. 76, 4025 (1954).

6 A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and O. A. Nesmeyanova, Dokl. Akad. Nauk SSSR 97, 459 (1954).

7 D. W. Mayo, P. D. Shaw and M. Rausch, Chem. & Ind. 1388 (1957).

It is soluble in benzene, cyclohexane, ether and alcohol, but not in water; ethanolic solutions decompose slowly.

The structure of nitroferrocene was demonstrated by its spectral properties and a derivative. An infrared spectrum of the compound (KBr pellet) shows bands at 1507 (nitro),[8] 1425, 1369, 1348, 1330, 1107 (unsubstituted cyclopentadienyl ring), and 820 cm^{-1} (ferrocene). Its ultraviolet spectrum, determined in ethanol, contains maxima at 242, 270 (Sh), 372 and 495 mμ. Reduction of nitroferrocene with iron and hydrochloric acid gives aminoferrocene,[9] sublimed sample m.p. 154° (lit.[10] m.p. 153-155°).

Studies are in progress concerned with other products from this and related reactions, as well as with additional physical and chemical properties of nitroferrocene.

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[8] L. J. Bellamy, The Infrared Spectra of Complex Molecules (2nd Ed.). John Wiley, New York (1958).

[9] The method of choice for the preparation of aminoferrocene has been shown recently to be the reaction of lithioferrocene with methoxyamine (L. Westman and K. L. Rinehart, Jr., Unpublished results).

[10] A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya and L. S. Shilovtseva, Dokl. Akad. Nauk SSSR 102, 535 (1955).

Tetrahedron Letters, No.12, pp. 18-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

STUDIES ON LOW-PRESSURE POLYMERIZATION OF ETHENE

THE INTERACTION OF $AlEt_2Cl$ AND $TiCl_4$. POLYMERIZATION OF ETHENE AT LOW TEMPERATURE; FORMATION OF BIFUNCTIONAL PRODUCTS

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(Shell Internationale Research Maatschappij N.V.)

(Received 17 July 1959)

POLYMERIZATION mechanisms are usually divided into three categories, according to the nature of the growing entities, viz. cationic, anionic and free radical. For various reasons, none of these seemed to hold in the case of Ziegler polymerizations. The presence of a new type of intermediate fragments therefore seemed likely.

The starting point of the present investigation was the interaction of the catalyst components mostly employed in the Ziegler polymerization of ethene, viz. diethylaluminium chloride and titanium tetrachloride.

Results

(1) Diethylaluminium chloride is usually represented by the formula $AlEt_2Cl$. Ebullioscopic determination of the molecular weight (in benzene) indicated that this compound is actually a dimer $(AlEt_2Cl)_2$.

(2) Interaction of $(AlEt_2Cl)_2$ and $TiCl_4$ in benzene solution at 25° C under nitrogen yielded a brown precipitate and gaseous products. At Al/Ti ratios of 0.5-3.3 mainly ethane was isolated (30-58% on Ti^{3+}

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* Present address: Leiden University.

formed) and only small amounts of hydrogen, butane and butene (total 1-3% on Ti^{3+}). At high Al/Ti ratios ethene was also formed (1-2% on Ti^{3+}).

The brown precipitate consists mainly of $TiCl_3$; in addition small amounts of polyethene (2-6 wt.%, 10-30% on Ti^{3+} calculated as C_2H_4), Al (2-4 wt.%) and Ti^{4+} (3-6 wt.%) are present even after thorough extraction with boiling benzene. Only very small amounts of ehtyl-aluminium compounds were found in the washed precipitate (0.1 wt.% C_2H_5). The filtrate contained most of the Al (>90% on intake) partly as unconverted AlEt compounds, partly in the form of organic Al compounds of higher molecular weight. The presence of the latter compounds was proved by oxygenation of the filtrate and subsequent hydrolysis of the solid Al-alkoxy compounds. Primary aliphatic alcohols were obtained with an average mol. wt. of 400. The amounts isolated in various experiments corresponded to 10-30% C_2H_4 on Ti^{3+}. The intake of ethyl equivalents could be nearly completely accounted for on the basis of ethane, ethene polymer of high mol. wt. and organic Al compounds. Analogous experiments with $(AlEt_2Cl)_2$ alone in the presence of ethene showed that in this case higher Al compounds are not formed. When the reaction is brought to completion all Ti is present in the precipitate (>95%). Both the filtrate and the washed precipitate are inactive with respect to ethene polymerization.

(3) Li-ethyl and $TiCl_4$ (Li/Ti = 1) gave, besides LiCl and $TiCl_3$ (52% on Ti intake), ethane (43.8% on Ti-intake), ethene (1.6%) and butane (0.5%). From the precipitate polyethene was isolated (the amount corresponded to 10% C_2H_4).

$(AlEtCl_2)_2$ and $TiCl_4$ (Al/Ti = 1) also gave $TiCl_3$ and ethane (39% on Ti^{3+}).

(4) Polymerization of ethene at $-10^{\circ}C$ with $(AlEt_2Cl)_2$ and $TiCl_4$ as catalysts mainly gave soluble low mol. wt. polymers (80% on ethene converted, average mol. wt. 400). Filtration of the reaction mixture under nitrogen and treatment of the filtrate with oxygen and subsequent hydrolysis yielded a fraction consisting only of alcohols (A, 70% on Ti intake) and a fraction consisting only of olefins (B, 470% on Ti intake). Distillation of A gave two alcohol fractions which contained about one double bond per two molecules (ozonometric and infra-red analysis, Table 1). The alcohols were exclusively primary alcohols.

TABLE 1. Composition of alcohols

B.p. fraction $^{\circ}C$/mm Hg.	% on A	% oxygen	average mol. wt.	oxygen atoms/mole	Double bonds/mole
80-140/0.1	31	6.5	271	1.10	0.40
140-200/0.1	27	4.9	337	1.03	0.67

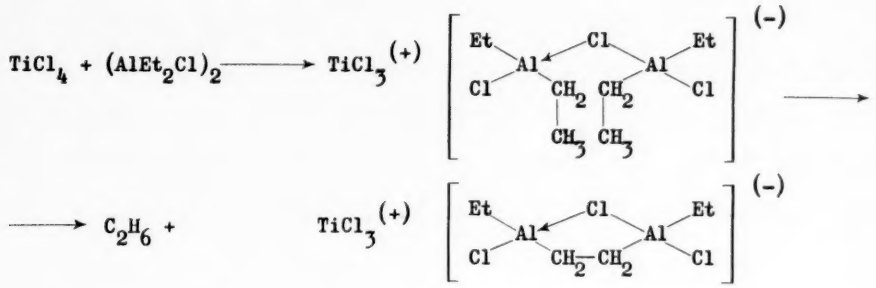
B was found to consist of a mixture of alkyl- and dialkyl-ethenes. On a molar basis the total amount of products was 5 times greater than the amount of $TiCl_4$ used. It was verified that with $(AlEt_2Cl)_2$ alone under the same conditions low mol. wt. polymers are not formed.

Discussion

A. Formation of ethane

The formation of ethane may have been due either to an intermolecular or an intramolecular process. Since little butane was formed free ethyl radicals cannot have been operative. This suggests ethane formation to be an intramolecular process, occurring simultaneously with ethyl

formation by abstraction of a hydrogen atom from another ethyl group in the Al-fragment:



I

Such a hydrogen abstraction process may be facilitated by the resonance stabilization of I, which may occur in the following way:

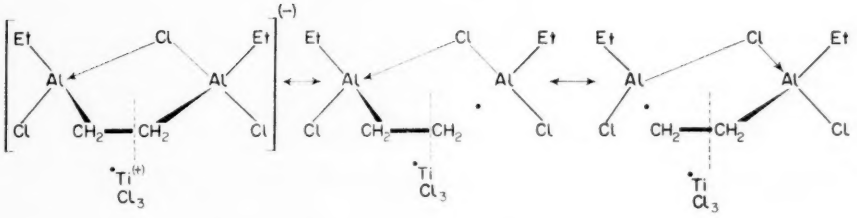


FIG. 1

It is seen that the essential hypothesis involved is the formation of an $>Al-CH_2-CH_2$ fragment which is stabilized by interaction with trivalent Al- and/or trivalent Ti-compounds.

We consider the stabilized fragment to be the initiating species for the polymerization of ethene (see B).

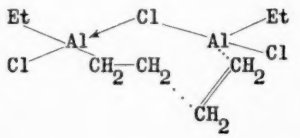
Similar structures may be written for the products formed by interaction of $TiCl_4$ and $(AlEtCl_2)_2$ or Li-Et.

The formation of polyethene and in some cases ethene upon interaction of $TiCl_4$ and $(AlEt_2Cl)_2$ may take place by decomposition of I with formation of unstable Al compounds or by reaction of I with another equivalent of $TiCl_4$:

$$I + TiCl_4 \longrightarrow 2\ TiCl_3 + (EtAlCl_2)_2 + C_2H_4.$$

B. Chain growth, termination and transfer in ethene polymerization

We assume chain growth to take place by a four-centre reaction between C_2H_4 and the long, weak $Al.CH_2$ or $Ti.CH_2$ bond of I, forming fragments of a similar resonance-stabilized structure as the initiating fragment:



Since a four-centre addition should be highly sensitive to steric influences - cf. Diels-Alder additions - this assumption might explain the high degree of stereo-specifity observed in polymerizations of this type.

In the absence of ethene the stabilized $>Al(CH_2)_n$ fragment disappears by disproportionation, producing Al-compounds which contain saturated as well as unsaturated alkyl groups:

$>Al-(CH_2)_n-CH_2-CH_3$ and $>Al-(CH_2)_n-CH=CH_2$. Upon addition of oxygen and subsequent hydrolysis these products give saturated and unsaturated alcohols.

The formation of several molecules of alkenes per molecule of $TiCl_4$ indicates that a transfer mechanism occurs. It may take place by interaction of ethene with the growing fragment, regenerating a primary initiating fragment I and a molecule of alkene.

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A NOVEL CATALYST SYSTEM FOR THE LOW-PRESSURE POLYMERIZATION OF ETHENE

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(Received 17 July 1959)

OUR assumptions with respect to the growing entities in the Ziegler polymerization[1] have led us to attempt generation of these fragments by other means. The partial reduction of aluminium trichloride with alkali metal in the presence of ethene, followed by oxidation with $TiCl_4$, was found to be successful.

Results

(1) $AlCl_3$ and K (1-2:1) suspended in heptane react in the presence of ethene with the formation of a black-grey solid reaction product; addition of $TiCl_4$ led to a rapid polymerization to polyethene (65°C, atmospheric pressure). The reactivity of the system increases to a maximum with increasing reaction time of $AlCl_3$ and K (1 hr). The reaction between $AlCl_3$ and K could also be carried out in a nitrogen atmosphere; however, polymerization took place only if the replacement of nitrogen by ethene was performed before the addition of $TiCl_4$.

(2) The black-grey product, isolated by filtration, has the same

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1 R. van Helden, A. F. Bickel, E. C. Kooyman, Tetrahedron Letters No. 12, 18 (1959).

reactivity in combination with $TiCl_4$ as the original system. Decomposition of this material with water gives ethane (about 50% on K-intake) and hydrogen (about 30% on K-intake). The amount of ethane formed amounted to 93% based on ethene absorbed during the reaction of $AlCl_3$ and K. With D_2O more than 90% of the deutero-ethanes produced had the composition $C_2H_4D_2$.

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By extraction of the black-grey solid with ether a white compound A was obtained (yield 45% on Al-intake) which had the composition (Table 1):

$Al_2Cl_4.C_2H_4.2Et_2O$ (A) m.p. 74.6-75.2°C (vacuo)

TABLE 1

	Mol. wt. (ebullioscopic)	% Al	% Cl	% C_2H_6	% Et_2O
Calc. for A	372.1	14.5	38.1	7.54	39.9
Found	364; 370	14.7	38.2	7.42	35 ± 4*

* Mean value from 6 determinations

Decomposition with D_2O yielded more than 90% $C_2H_4D_2$. The ether-insoluble part, a black material, mainly consisted of Al and/or Al subhalides.

When the dietherate (A) was allowed to react with $TiCl_4$ in the presence of ethene no polymerization took place, but when 2 moles of $AlCl_3$/mole of A were added, addition of $TiCl_4$ led to a rapid polymerization to polyethene.

Interaction of the black-grey solid or compound A + 2 $AlCl_3$ with $TiCl_4$ under nitrogen yields $TiCl_3$ and small amounts of ethene. Ethane was not formed.

Discussion

Since interaction of $AlCl_3$ and K under nitrogen and replacement by ethene shortly before addition of $TiCl_4$ gives the same results as when

carrying out the whole reaction under ethene, primary formation of Al-subhalides and/or Al would seem probable. Their presence is confirmed by the formation of hydrogen on decomposition with water.

The subhalides formed react with ethene to form compounds of the type

$$AlCl_2\text{-}C_2H_4\text{-}AlCl_2 \qquad (B)$$

The proposed structure of (A):

$$\begin{matrix} Cl \\ Cl \end{matrix} \; Al \; CH_2 \; CH_2 \; Al \; \begin{matrix} Cl \\ Cl \end{matrix} \qquad 2\ Et_2O$$

is supported by the formation of $C_2H_4D_2$ on decomposition with D_2O and by the known structure of the analogous boron compound $Cl_2B\text{-}C_2H_4\text{-}BCl_2$.[2]

When $TiCl_4$ is added before nitrogen has been replaced by ethene, the subhalides are oxidized to $AlCl_3$ and the formation of (B) is hence not possible: polymerization does not take place.

It seems reasonable to assume that on addition of $TiCl_4$ the initiating fragments (See ref. 1) are formed in the following way:

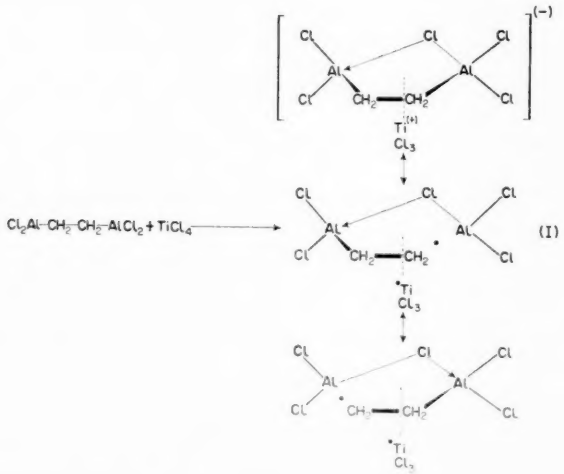

FIG. 1

A comparison of this reaction with that postulated in ref. 1 shows that a similar type of initiating species is formed in both cases. The formation of ethene is probably due to decomposition of I or by reaction with another equivalent of $TiCl_4$ in the same way as mentioned in ref. 1.

The activation of the system A + $TiCl_4$ by $AlCl_3$ is apparently due to the following reaction:

$$2\ AlCl_3 + Cl_2Al\text{-}C_2H_4\text{-}AlCl_2.2\ Et_2O \longrightarrow 2\ AlCl_3\text{-}Et_2O + Cl_2Al\text{-}C_2H_4\text{-}AlCl_2$$

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[2] W. H. Urry et al., J. Amer. Chem. Soc. 76, 5299 (1954); E. B. Moore and W. N. Lipscomb, Acta Cryst. 9, 668 (1956).

A list of papers recently accepted for publication in "Tetrahedron"

A. BOWERS, E. DENOT, R. URQINZA and L. M. SANCHEZ-HIDALGO: Steroids-CXXVI Some fission reactions of steroid 5,6-epoxides induced by boron trifluoride etherate.

U. RAMDAS NAYAK and SUKH DEV: Studies in sesquiterpenes-XVII. Hydration of longifolene.

A. FREGDA: Steric correlations by the quasi-racemate method.

W. COCKER, W. J. DAVIS, T. B. H. McMURRY and P. A. START: Furan tetracarboxylic acid.

J. W. POWELL and M. C. WHITING: The decomposition of sulphonylhydrazone salts. Mechanism and stereochemistry.

L. H. BRIGGS, R. C. CAMBIE, R. N. SEELYE and A. D. WARTH: Chemistry of the podocarpaceae-IV. Constituents of the heartwood of Podocarpus dacrydiodes A. Rich.

A. L. NUSSBAUM and F. E. CARLON: cis-trans Isomerism of steroidal $\Delta^{17(20)}$-enol acetates.

SHIGEHIKO SUGASAWA and HIROSHI YOSHIKAWA: A synthesis of DL-15,16-dimethoxyerythrinane.

R. D. BROWN and R. D. HARCOURT: A theoretical study of the chemistry of isoquinoline.

J. JACQUES, C. WEIDMANN et L. CHANH BINH: Structure moléculaire et activité oestrogène-XIX. Préparation stéréo-sélective des acides méthyl-2(methoxy-6'-naphtyl-2')-3 pentanoïques thréo et érythro.

F. M. BERINGER, P. S. FORGIONE and M. D. YUDIS: Diaryliodonium salts-XII. The phenylation of dimedone, dibenzoylmethane and tribenzoylmethane.

S. F. BIRCH, T. V. CULLUM, R. A. DEAN and D. G. REDFORD: Sulphur compounds in the kerosine boiling range of Middle East distillates. Occurrence of a bicyclic thiophene and a thienyl sulphide.

M. E. VOLPIN, D. N. KURSANOV and V. G. DULOVA: New mutual conversion of aromatic systems. Tropilium salts and benzene.

1959

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THE OXIDATIVE REARRANGEMENT OF KETONES TO CARBOXYLIC ACIDS

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THE interaction of hydrogen peroxide and selenium dioxide with olefins yields 1,2-[1] and 1,3-[2] glycols. Use of these reagents with cyclic ketones[3] gives cycloalkanecarboxylic acids by oxidative ring contraction.

We now wish to report that open-chain ketones also rearrange. Details of the treatment of acetone and phenylacetone are given below. Acetone was converted to propionic acid (39%), identified as the ethyl ester. Phenylacetone rearranged predominantly to hydratropic acid (11%) and to a slight extent to hydrocinnamic acid (0.6%), identified as the methyl esters.

We have also found that substitution of selenic acid and pyridine for selenium dioxide gives superior yields of ring contraction products. For example, cyclohexanone and excess hydrogen peroxide with approximately 3 mol % selenic acid and 10 mol % pyridine produced 64% cyclopentane-carboxylic acid. Competition by ring enlargement (Baeyer-Villiger), previously undetected,[3] was evidenced by the isolation of 10-30% ethyl 6-hydroxycaproate.

We are continuing our study of the scope and mechanism of this reaction.

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[1] P. Seguin and M. Delepine, C. R. Acad. Sci., Paris 216, 667 (1943); M. Mugdan and D. P. Young, J. Chem. Soc. 2988 (1949).

[2] A. Stoll, A. Lindenmann and E. Jucker, Helv. Chim. Acta 36, 268 (1953).

[3] G. B. Payne and C. W. Smith, J. Org. Chem. 22, 1680 (1957).

Experimental

Oxidation of acetone

A solution of acetone (29 g, 0.5 mole), t-butyl alcohol (150 ml), 30% hydrogen peroxide (100 ml, 1 mole) and selenic acid (sp. gr. 1.4, 4 ml) was refluxed for 6 hr, made strongly alkaline with 40% potassium hydroxide solution, refluxed for an additional hour, and t-butyl alcohol was removed by steam distillation. The acids were isolated by acidification, steam distillation, salting-out, and ether extraction. Distillation of the ethyl esters gave A, b.p. 75-80°, 19 g; B, b.p. 80-99°, 8 g; residue, 2 g. Distillation of the residue gave C, b.p. 98-9°, 1 g. Gas chromatography of the distillates showed an over-all composition of 20% ethanol, 9.6% ethyl acetate and 71% ethyl propionate (39% based upon acetone), and about 0.1% of unidentified material. Fraction C, which was 96% ethyl propionate, formed a p-toluide,[4] m.p. 125-6° (lit.[5] m.p. 126°), undepressed when mixed with an authentic sample.

Oxidation of phenylacetone

A two-phase mixture of phenylacetone (34 g, 0.25 mole), t-butyl alcohol (150 ml), 30% hydrogen peroxide (50 ml, 0.5 mole), selenic acid (sp.gr. 1.4, 4 ml) and pyridine (4 ml) was refluxed for 21 hr, treated with 100 ml of 30% potassium carbonate solution, and extracted with ether. The acids were isolated by acidifying the aqueous solution and extracting with chloroform. Vacuum distillation of the methyl esters gave 5 g of product, shown by gas chromatography to consist of 87% methyl hydratropate (11% based upon phenyl-

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[4] S. S. Jenkins, J. Amer. Chem. Soc. 55, 3049 (1933).

[5] C. A. Bischoff, Liebigs Ann. 279, 172 (1894).

acetone), 5.1% methyl hydrocinnamate (0.6% based upon phenylacetone), 6.6% methyl benzoate and 1.3% methyl phenylacetate. Treatment with benzylamine[6] gave a benzylamide, m.p. 78.5-9.5°, which showed no depression when mixed with an authentic sample prepared from hydratropic acid (Found: C, 80.84; H, 7.14; N, 6.01. $C_{16}H_{17}NO$ requires C, 80.32; H, 7.16; N, 5.86%).

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[6] O. C. Dermer and J. King, J. Org. Chem. 8, 168 (1943).

Tetrahedron Letters, No. 13, pp. 4-10, 1959. Pergamon Press Ltd. Printed in Great Britain.

DOUBLET CHARACTER OF O-H ABSORPTION IN SATURATED ALCOHOLS*

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(Received 3 August 1959)

CONSIDERABLE attention has been directed recently to the doublet character of the O-H stretching absorption of monomeric unsaturated alcohols.[1] The two absorption bands can be ascribed to different species containing free and π-hydrogen bonded hydroxyl groups, respectively. It seems to be not as well recognized, however, that doublet O-H absorption can be displayed by saturated alcohols as well.[2] For example, this was observed in the second overtone region for several primary alcohols by Badger,[2a] and by Tuomikoski and Toivonen[2b] for ethanol, borneol and the epimeric fenchols.

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* Research sponsored by the Office of Ordnance Research, U.S. Army.

** National Science Foundation Predoctoral Fellow, 1958-1959.

[1a] I. M. Goldman and R. O. Crisler, J. Org. Chem. 23, 751 (1958);

[b] P. Schleyer, D. S. Trifan and R. Bacskai, J. Amer. Chem. Soc. 80, 6691 (1958) and references cited therein; D. S. Trifan, R. Bacskai, P. Schleyer and C. Wintner, Abstracts 135th Meeting of American Chemical Society, p. 98-O. April 5-10, 1959, Boston, Mass.

[2a] R. M. Badger and S. H. Bauer, J. Chem. Phys. 4, 711 (1936);

[b] P. Tuomikoski, Suomen Kemistilehti 23B, 44 (1950) and references cited therein; P. Tuomikoski, E. Pulkkinen, P. Hirsjärvi and N. J. Toivonen, Ibid. 23B, 53 (1950).

In the present work, some seventy saturated alcohols were investigated conveniently in dilute solution in carbon tetrachloride, using 10 cm matched quartz cells on the Cary Model 14 spectrophotometer in the first overtone 1.4μ region, where the separation between component bands is relatively large and bands associated with strong intermolecular hydrogen bonds are absent.

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Most of the compounds exhibited hydroxyl absorption of the general type illustrated in Fig. 1, the component bands being separated graphically and the relative intensities of absorption (relative areas, $\underline{B}_1/\underline{B}_2$) approximated without correction for the band wings. Some examples are summarized in Table 1. In representative cases, e.g., 2-propanol, 3-pentanol and 3-phenylpropanol-1, it was demonstrated that the relative band intensities were independent of concentration from that commonly employed, 0.01-0.02 M, down to 0.001 M. Deuterated 2-propanol-d exhibited an absorption doublet similar to that of 2-propanol in the corresponding 1.9μ region. With ethanol, 2-butanol, 2-pentanol, 3-pentanol and t-butyl alcohol, it was observed that the O-H absorption pattern in the second overtone 0.9μ region was analogous to that at 1.4μ.

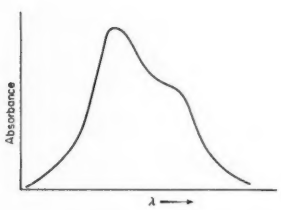


FIG. 1. Schematic illustration of O-H absorption band.

TABLE 1. Infrared absorption of some alcohols (ca. 0.01 M) in CCl_4 solution in the first overtone

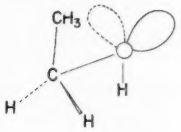
Compound	λ-max, Å					
	1[a]	2[b]	3[a]	B_1/B_2	B_1/B_3	, cm^{-1}
CH_3OH	14042	—	—	--	--	--
CH_3CH_2OH	14081	14130	—	7.92	--	24.5
$(CH_3)_2CHOH$	14110	14179	--	7.56	--	33
$(CH_3)_3COH$	14157	—	--	—	--	—
$(CH_3)_2CHOD$	18996	19082	--	1.85	--	23
F_3CCH_2OH	14068[b]	14132[a]	—	0.135	--	32
$CH_3CH_2CH(OH)CH_3$	14110	14194	—	5.64	--	42
$CH_3(CH_2)_2CH(OH)CH_3$	14110	14190	—	5.84	--	40
$(C_2H_5)_2CHOH$	14100	14204	—	5.86	—	52
$ClCH_2CH_2OH$	14083	14140	14227	9.16	0.462	28.5,72
$C_6H_5CH_2CH_2OH$	14080	14130	14209	1.41	0.934	24, 64.5

[a] ± 2 Å

[b] ± 5 Å

The most obvious cause of the splitting observed for the saturated alcohols[2a] is conformational heterogeneity. In the series, MeOH, EtOH, i-PrOH and t-BuOH, this depends solely on rotation about the C-O bond and is thus absent in the symmetrical members of the series, MeOH and t-BuOH. With EtOH and i-PrOH, two conformations are expected, these being illustrated for EtOH, Correspondingly, MeOH and t-BuOH show singlet O-H absorption, while EtOH and i-PrOH display a doublet (Table 1).

Trifluoroethanol displays doublet absorption analogous to that of ethanol except for a reversal of relative band intensities (Table 1).



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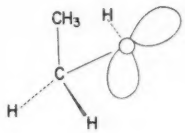

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Other primary alcohols, e.g., 1-propanol, isobutyl alcohol, 1-octanol and neopentyl alcohol, are analogous to ethanol, $\Delta\nu$ being ca. 25 cm^{-1}. Secondary alcohols in general show doublet absorption as does 2-propanol, but the $\Delta\nu$ is quite variable, the largest value so far observed being the 52 cm^{-1} displayed by 3-pentanol (Table 1).

It is not yet clear just when the possibility of conformational heterogeneity can be expected to lead to doublet O-H absorption. For example, in the series, $(CH_3)_2C(OH)R$, singlet absorption is observed for R=ET, just as for Me, but a doublet is present for R=i-Pr. Also, methylcyclobutylcarbinol shows singlet absorption, even though methylisopropylcarbinol shows a doublet. Finally, cyclopentanol shows a single band, whereas cyclohexanol and cyclodecanol display doublet absorption. Further, it is not clear whether conformational heterogeneity of saturated alcohols will lead to still greater multiplicity of O-H absorption bands, since no clear case of this has been observed.

The indications are that there will be sufficient regularity of behavior of alicyclic and bicyclic alcohols to make the doublet character of the O-H absorption useful for diagnosis of configuration and conformation.

Thus in cyclohexanols which are relatively homogeneous with respect to the conformational disposition of the oxygen atom[3], those with an equatorial hydroxyl group, e.g., trans-2-methylcyclohexanol, trans-4-t-butylcyclohexanol, 3β-cholestanol and menthol, show doublet O-H absorption. On the other hand, those with an axial hydroxyl group, e.g., cis-2-cyclohexylcyclohexanol, neomenthol and cis-4-t-butylcyclohexanol, exhibit a single absorption band. With bicyclic compounds, those closely related to exo-2-norborneol (I, II[4], III[5], IV[5], V[6], VI[5], VII[6]) all show only single bands. Similarly, 7-norborneol (VIII) exhibits a single O-H absorption. However, those compounds related to endo-2-norborneol (IX, X[5], XI[5], XII[6], XIII[6], XIV[6]) all exhibit doublets.

There are, however, limitations to the above generalizations, in that increased steric congestion in the axial-cyclohexanols can convert the singlet to a doublet, e.g., in cis-2-t-butylcyclohexanol. Similarly, vicinal methyl substitution on exo-2-norborneol induces doublet character in the O-H absorption, e.g., in exo-camphenilol[6] (XV). The behavior of the epimeric bicyclo[3.2.0.]heptan-2-ols[7] (XVI and XVII) may be considered analogous, the trans-epimer XVI showing singlet, the cis-epimer XVII exhibiting doublet absorption. Distortion of the exo-2-norborneol structure can also convert singlet to doublet absorption, as in the case of the half-cage alcohol[5] XVIII.

With alcohols in which intramolecular hydrogen bonding is possible,

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[3] S. Winstein, and N. J. Holness, J. Amer. Chem. Soc. 77, 3054 (1955).

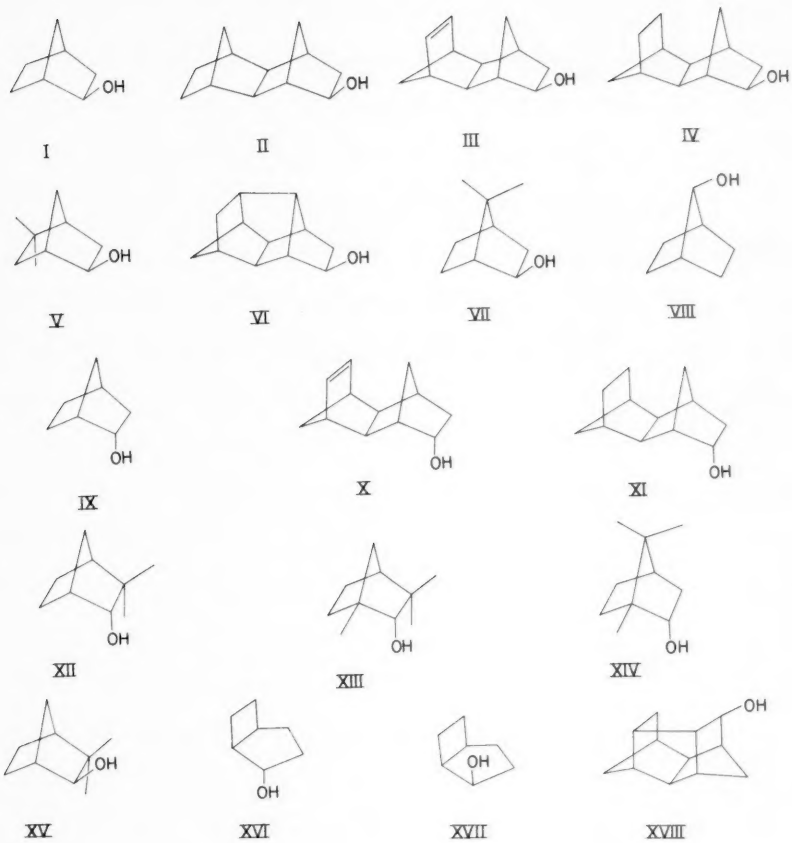
[4] S. B. Soloway, J. Amer. Chem. Soc. 74, 1027 (1952).

[5] S. Winstein, Experientia Supplementum II 137 (1955).

[6] S. Winstein, Abstracts 15th Nat. Org. Chem. Symposium of American Chemical Society, p. 29. June 17-20, 1957, Rochester, N.Y.

[7] S. Winstein, F. Gadient, E. T. Stafford and P. E. Klinedinst, Jr., J. Amer. Chem. Soc. 80, 5895 (1958).

three components to the monomeric O-H absorption are often observed.[8] An example is ethylene chlorohydrin[9] (Table 1), two of the bands being analogous



[8] R. Piccolini and J. Sonnenberg, unpublished work.

[9] L. R. Zumwalt and R. M. Badger, J. Amer. Chem. Soc. 62, 305 (1940).

to those of ethanol and the third at higher wavelength being due to those of the conformations which are gauche with respect to rotation about both the C-C and C-O bonds which have syn chlorine and hydroxyl hydrogen atoms for hydrogen bonding. The case of 2-phenylethanol[8] is quite analogous (Table 1).

The demonstration that doublet character of the O-H absorption is quite general for saturated alcohols has obvious implications for the interpretation of the spectra of unsaturated alcohols,[8] e.g., benzyl alcohol[1b,10] or allyl alcohol,[1b] which show doublet absorption, since neither of the two bands need necessarily be associated with an attractive hydrogen bonding interaction. Other criteria for intramolecular hydrogen bonding, besides doublet character of the O-H absorption, must be employed.[8]

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[10] J. J. Fox and A. E. Martin, Trans. Faraday Soc. 36, 897 (1940).

Tetrahedron Letters No. 13, pp.11-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

NATURALLY OCCURRING OXYGEN HETEROCYCLICS

4-PHENYL-5,7-DIHYDROXY-6-ISOVALERYL-8-ISOPENTENYLCOUMARIN

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(Received 24 July 1959)

IN a recent communication[1] from this Laboratory it was shown that the insecticidal constituent[2] mammein from the seeds of Mammea americana L. possesses structure I. Through the kind co-operation of Dr. Murrell P. Morris of the U.S. Department of Agriculture Experiment Station in Mayaguez, Puerto Rico, we have obtained a supply of a yellow toxic principle derived from the pulp of the fruits of the same plant, and the present report is concerned with its structure elucidation.

Chromatographic purification of the yellow substance and repeated recrystallization from various solvents led to homogenous material with a wide melting point range, apparently due to solvation. The analytical

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1 Paper V: C. Djerassi, E. J. Eisenbraun, R. A. Finnegan and B. Gilbert, Tetrahedron Letters No. 1, 10 (1959).

2 M. P. Morris and C. Pagan, J. Amer. Chem. Soc. 75, 1489 (1953).

specimen (from aqueous ethanol) exhibited m.p. 98-109° (after drying at room temperature in vacuo), $\lambda_{max}^{EtOH-HCl}$ 282 and 339 mμ (log ε 4.49 and 4.13), λ_{min}^{EtOH} 249.5 and 320 mμ (log ε 4.09 and 4.07), $\lambda_{max}^{CHCl_3}$ 2.91, 3.04, 5.78, 6.17 and 6.30 μ, and gave a dark brown color with ferric chloride solution. The analytical results (Found: C, 74.42; H, 6.47; O, 19.26) were consistent with the empirical formula $C_{25}H_{26}O_5$ and this was confirmed by the preparation of the beautifully crystalline diacetate IIb (m.p. 122-124°; Found for $C_{29}H_{30}O_7$: C, 71.00; H, 6.20; O, 22.99) and dimethyl ether IIc (m.p. 86-89°; Found for $C_{27}H_{30}O_5$: C, 74.61; H, 6.71; O, 18.26; methoxyl, 14.47).

The analytical and spectral data suggested a coumarin skeleton, similar to that of mammein (I).[1] When the parent phenol IIa was heated under reflux for 67 hr with 15% potassium hydroxide solution, there were isolated isovaleric acid, acetophenone and isopentenylphloroglucinol (IIIa) (m.p. 101-102°; Found for $C_{11}H_{14}O_3$: C, 67.97; H, 7.26; O, 25.06). The structure of this phenol followed from its ultraviolet absorption spectrum (λ_{max}^{MeOH} 271, 274 and 279 mμ, log ε 2.84, 2182 and 2.76; $\lambda_{max}^{MeOH-NaOH}$ 257, 279 and 355 mμ), typical of monoalkyl phloroglucinols[3] and from the formation of isopentylphloroglucinol (IIIb)[4] upon hydrogenation. The precise location of the double bond was established by ozonolysis of the parent compound IIa, which yielded acetone (69% yield as 2,4-dinitrophenylhydrazone) unaccompanied by formaldehyde.

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[3] T. W. Campbell and G. M. Coppinger, J. Amer. Chem. Soc. 73, 2708 (1951).

[4] T. S. Kenny, A. Robertson and S. W. George, J. Chem. Soc. 1601 (1939).

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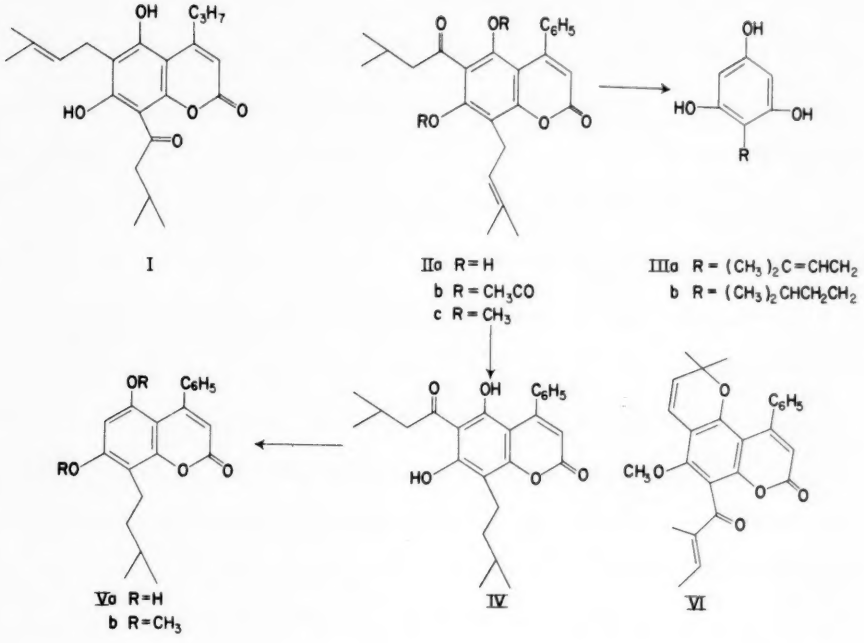

The precise skeletal structure and the disposition of the substituents was demonstrated as follows. Hydrogenation of IIa with palladized charcoal resulted in the uptake of one equivalent of hydrogen with the production

of a yellow dihydro derivative IV (m.p. 99 - 103°), whose relevant ultraviolet and infrared spectral bands coincided with those of IIa. Deacylation of the dihydro compound IV with 75% sulfuric acid[5] provided 4-phenyl-5,7-dihydroxy-8-isopentylcoumarin (Va) (m.p. 184-186°, λ_{max}^{EtOH} 266 and 338 mμ, log ε 4.08 and 4.04; Found for $C_{20}H_{20}O_4$: C, 74.15; H, 6.43; O, 19.69), which was methylated with dimethyl sulfate in acetone solution in the presence of potassium carbonate to give 4-phenyl-5,7-dimethoxy-8-isopentylcoumarin (Vb) (m.p. 131-132°; Found for $C_{22}H_{24}O_4$: C, 74.95; H, 6.63; O, 18.36; methoxyl, 17.24). Its constitution was proved by Pechmann condensation of 2-isopentyl-3,5-dimethoxyphenol (m.p. 56-57°)[6] with ethyl benzoylacetate which furnished the identical dimethyl ether (Vb).

The above results are only consistent with the structure of 4-phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin (IIa) for the toxic constituent of the pulp of the mamey fruit. Naturally occurring 4-substituted coumarins are very rare and the isolation of mammein (I) and IIa from the same plant is of some biogenetic interest. It is pertinent to mention that only three other substituted 4-phenylcoumarins have been encountered in nature, namely dalbergin,[7] dalbergin methyl ether (4-phenyl-6,7-dimethoxycoumarin)[7] and calophyllolide (VI).[8]

[5] Deacylation under these conditions does not cause any rearrangement, since the coumarin ring is not opened (see ref. 1).

[6] To be published.

[7] V. K. Ahluwalia and T. R. Seshadri, J. Chem. Soc. 970 (1957).

[8] J. Polonsky, Bull. Soc. Chim. Fr. 929 (1958).

The latter shows considerable structural resemblance to the presently described coumarin IIa and it should be noted that both plant sources (*Calophyllum inophyllum* L. and *Mammea americana* L.) belong to closely related genera of the same familiy (*Guttiferae*).

Financial assistance was generously provided by the National Heart Institute (grant No. H-2574) of the National Institutes of Health, U.S. Public Health Service.

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THE RELATION OF FABACEIN TO CUCURBITACIN B

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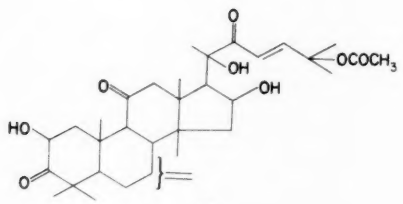
(Received 27 July 1959)

TWO crystalline compounds have been isolated from Echinocyctis fabacea, cucurbitacin B and fabacein.[1] Cucurbitacin B appears to have the molecular formula $C_{32}H_{46}O_8$, and structural formula I recently has been proposed for it.[2] Fabacein originally was assigned the molecular formula $C_{30}H_{44}O_8$.[1]



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[1] W. O. Eisenhut and C. R. Noller, J. Org. Chem. 23, 1984 (1958).

[2] We wish to thank Dr. P. R. Enslin for a copy of a communication submitted to Chem. & Ind. by D. Lavie, Y. Shvo, D. Willner, P. R. Enslin, J. M. Hugo and K. B. Norton in which this formula is proposed.

We wish now to report that fabacein is a diacetate having the molecular formula $C_{34}H_{48-50}O_9$, the original analyses agreeing equally well with this formula (Calc. for $C_{34}H_{48}O_9$: C, 67.98; H, 8.05; for $C_{34}H_{50}O_9$; C, 67.75; H, 8.36. Found: C, 67.56; H, 8.23; average of 10 analyses). Like cucurbitacin B, fabacein contains an α,β-unsaturated carbonyl group and at least one free hydroxyl group.[1] Moreover, 1.3 moles of hydrogen are absorbed on catalytic hydrogenation in ethanol using palladium-on-carbon catalyst to give two products which readily can be separated. One product is dihydrofabacein (Calc. for $C_{34}H_{50}O_9$: C, 67.75; H, 8.36; for $C_{34}H_{52}O_9$: C, 67.52; H, 8.67. Found: C, 67.70; H, 8.33); m.p. 177-179° from acetone-ether-hexane; $[\alpha]_D^{25}$ + 24.0° (c = 1.35);[3] UV, λ_{max} 285 mμ, log ε 2.39;[3] IR, 2.90 (OH) 5.75-5.79 (OAc), 5.85 (C=O), 8.05 (OAc).[3] The second product could not be crystallized, but its paper chromatogram indicated that it was homogeneous. Analysis showed that it is a dihydromonodeacetoxyfabacein (Calc. for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88; for $C_{32}H_{50}O_7$: C, 70.30; H, 9.22. Found: C, 70.26; H, 8.83); $[\alpha]_D^{25}$ + 17.6° (c = 1.42); UV, λ_{max} 286 mμ, log ε 2.32; IR, 2.90 (OH), 5.78 (OAc), 5.85-5.89 (C=O), 8.05 (OAc). These products are analogous to those obtained by the hydrogenation of cucurbitacin B.[4]

Acetylation of fabacein and its hydrogenation products with acetic anhydride in pyridine gave only amorphous products which were purified by

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[3] All rotations and IR spectra are taken in chloroform and all UV spectra in ethanol.

[4] A. Melera, W. Schlegel, and C. R. Noller, J. Org. Chem. 24, 291 (1959).

passing through a chromatographic column. Each of the acetylated products was different from the corresponding product from cucurbitacin B. Fabacein gave an amorphous tetraacetate (Calc. for $C_{38}H_{52}O_{11}$: C, 66.65; H, 7.65; for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92. Found: C, 66.52; H, 8.05); $[\alpha]_D^{25}$ -2.0° (c = 1.76); UV, λ_{max} 229 mμ, log ε 4.24 and 289 mμ, log ε 2.49; IR, 2.95 (OH), 5.80 (OAc), 5.92, 6.15 (C=C-C=O), 8.05 (OAc). Dihydrofabacein also gave an amorphous tetraacetate (Calc. for $C_{38}H_{54}O_{11}$: C, 66.45; H, 7.92; for $C_{38}H_{56}O_{11}$: C, 66.25; H, 8.20. Found: C, 66.08; H, 8.19); $[\alpha]_D^{25}$ -8.0° (c = 1.35); UV, λ_{max} 282 mμ, log ε 2.49; IR, 2.95 (OH), 5.80 (OAc), 5.90 (C=O), 8.10 (OAc). The dihydromonodeacetoxyfabacein gave an amorphous triacetate (Calc. for $C_{36}H_{52}O_9$: C, 68.76; H, 8.34; for $C_{36}H_{54}O_9$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.70); $[\alpha]_D^{25}$ -13° (c = 1.15); UV, λ_{max} 287 mμ, log ε 2.37; IR, 2.95 (OH), 5.80 (OAc), 5.90 (C=O), 8.10 (OAc).

Oxidation of the acetylated dihydrodeacetoxyfabacein with chromium trioxide in acetic acid at room temperature gave a volatile acid identified as isocaproic acid by gas chromatography. The components of the neutral fraction from the oxidation were the same as those obtained by the oxidation of acetylated dihydrodeacetoxycucurbitacein B, the chief products being the ketones A and B.[4] Thus it appears that the difference between cucurbitacin B and fabacein lies in the structure of the side chain, although the carbon skeleton of isocaproic acid is present in both.

Other differences in the behavior of fabacein and cucurbitacin B have been observed. Thus cucurbitacin B undergoes rearrangement on acetylation as shown by the fact that hydrogenation of the tetraacetate gives a single amorphous product which is not identical with the product of acetylation of dihydrocucurbitacin B but is isomeric with it (Calc. for $C_{38}H_{54}O_{11}$: C,

66.45; H, 7.92; for $C_{38}H_{56}O_{11}$: C, 66.26; H, 8.19. Found: C, 66.25; H, 8.26); $[\alpha]_D^{25}$ + 3.5° (c = 1.49); UV, λ_{max} 286 mμ, log ε 2.43; IR 2.90 (OH), 5.80 (OAc), 5.90 sh (C=O), 8.10 (OAc). Hydrogenation of the tetraacetate of fabacein gives two products which are identical with acetylated dihydrofabacein and acetylated dihydrodeacetoxyfabacein. Moreover, the oxidations of these two compounds with chromium trioxide at room temperature do not yield carbon dioxide whereas the corresponding derivatives of cucurbitacin B do.

Acknowledgment - This investigation was supported (in part) by a PHS research grant, RG-5076, from the National Institute of Health, U.S. Public Health Service.

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SECONDARY ISOTOPE EFFECTS AND AROMATIC HYDROGEN EXCHANGE*

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(Received 4 August 1959)

IT has recently been demonstrated that secondary hydrogen isotope effects are absent from aromatic substitution by nitronium ion, mercuric ion, and molecular bromine.[1**] All evidence bearing on the mechanisms of these three reactions is consistent with a two-step reaction sequence having a single intermediate species for the actual substitution process.[3] Another type of aromatic substitution reaction, however, is thought to exist: the evidence concerning electrophilic substitution by hydrogen appears to

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* Work carried out under the auspices of the U.S. Atomic Energy Commission.

** The secondary isotope effect of 1.046 for bromination cited in this reference is now open to doubt: the expected large primary isotope effect in side chain bromination[2] could well account for all of the observed effect, even if only a relatively small amount of benzyl bromide were formed.

1 C. G. Swain, T. E. C. Knee and A. J. Kresge, J. Amer. Chem. Soc. 79, 505 (1957).

2 K. B. Wiberg, Chem. Rev. 55, 713 (1955).

3 C. K. Ingold, Structure and Mechanism in Organic Chemistry, p. 279. Cornell Univ. Press, Ithaca, New York (1953); P. W. Robertson, J. Chem. Soc. 1267 (1954); P. B. D. de la Mare, T. M. Dunn and J. T. Harvey, Ibid. 923 (1957); H. Zollinger, Experientia 12, 165 (1956); A. J. Kresge, unpublished work on mercuration.

demand a reaction sequence of at least three steps with at least two intermediate species along the reaction path.[4] We undertook to determine whether a secondary isotope effect would appear in this other type of aromatic substitution.

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We measured the rate of exchange of tritium at 25° between 9.58 M sulfuric acid ($\sim$ 62 weight %) and both ordinary toluene and toluene-α-d_3 (97 at.% deuterium in the methyl group). Tritium was present initially in the acid. Ortho- and para-substitution in this reaction are known to occur forty times as fast as meta-substitution.[5] The rates measured were, therefore, essentially those for ortho- and para-substitution.* Fig. 1 shows that substitution in both light and heavy toluene occurred at the same rate. Rate constants calculated by the usual least squares method are k_H = 0.936 cpm/min. σ = 0.019; k_D = 0.935 cpm/min. σ = 0.018 (σ is the standard deviation). This gives an isotope rate ratio of 1.002, σ = 0.026.

The absence of a secondary isotope effect in this reaction is consistent with data on other aromatic substitutions[1] and suggests the general absence of such effects in this large class of reactions. The usually accepted explanation[6] of secondary isotope effects is one involving hyperconjugation, and these effects would seem to be expected whenever hyperconjugative

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* The exchange was only taken to ca. 3% completion, the rate constants being obtained from direct plots of the amount of reaction vs. time. This procedure (valid for initial slopes only) avoids the necessity of knowing the position of exchange equilibrium.

4 V. Gold and D. P. N. Satchell, J. Chem. Soc. 3609, 3619, 3622 (1955); Ibid. 1635 (1956).

5 V. Gold and D. P. N. Satchell, J. Chem. Soc. 274 (1956).

6 E. S. Lewis, Tetrahedron 5, 143 (1959); V. J. Shiner, Jr., Ibid. 5, 243 (1959).

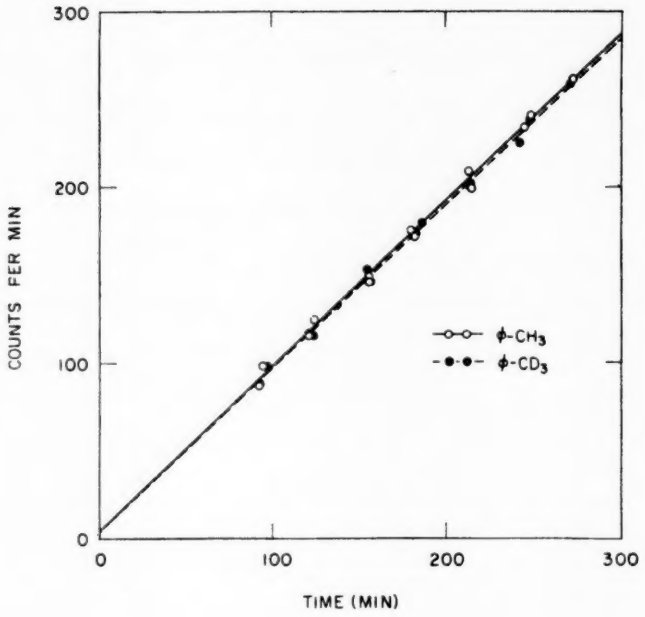

FIG. 1. Rates of nuclear hydrogen exchange of toluene and toluene-α-d_3 with 9.58 M sulfuric acid-t at 25°.

effects are important. And yet, it can be demonstrated that carbon-hydrogen hyperconjugation is at least as important an activating influence in aromatic substitution as it is in those solvolytic reactions where most secondary isotope effects have been found.*

* For example, application of a method recently developed by Taft and Lewis[7] which permits quantitative estimate of the hyperconjugative

An attempt has recently been made to rationalize this anomaly by invoking different degrees of electron release for C-H and C-D bonds.[8] This leads to an inductive contribution to the secondary isotope effect of a methyl group opposite in sign to the hyperconjugative contribution, and these two effects are said to be nicely balanced in aromatic substitution. It has recently been demonstrated, however, that any difference in inductive electron release between C-H and C-D bonds cannot possibly be large enough to accomodate this explanation.**[9]

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The anomaly, therefore, remains. And the fact that it exists at all makes it desirable to emphasize the danger of a too facile identification of secondary isotope effects with hyperconjugative phenomena, for it appears that the latter may be present without necessarily giving rise to the former.

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effect of a methyl group on a reaction, and which expresses the magnitude of this effect in terms of a parameter, R, discloses that aromatic bromination by molecular bromine has the remarkably high R value of 2.9. R values for aromatic hydrogen exchange, nitration, and mercuration are 1.8, 1.5, and 1.4 respectively, whereas R values for solvolytic reactions of benzhydryl and dimethylbenzyl chlorides range from 1.2 to only 1.4.

** Moreover, when Taft's method for quantitative evaluation of inductive effects[7,10] is applied to the cases in question, I values ranging from 0.10 to 0.19 are obtained for the solvolytic reactions, and 0.10 to 0.45 (bromination), for the aromatic substitutions. The ratios of the R values cited above to these I values will measure the relative contribution of hyperconjugative to inductive effects. These ratios are not significantly different for the two classes of reactions: 6.5 to 14 for solvolysis and 6.3 to 18 (hydrogen exchange) for aromatic substitution. Any small difference, in fact, points to the greater relative importance of hyperconjugation in aromatic hydrogen exchange.

7 R. W. Taft, Jr. and I. C. Lewis, Tetrahedron 5, 210 (1959).

8 E. A. Halevi and M. Nusim, Bull. Res. Counc. Israel 5A, 263 (1956); Abstrs. 16th Intl. Cong. Pure Appl. Chem. II, p. 27 (1957); E. A. Halevi, Tetrahedron 1, 174 (1957); Trans. Faraday Soc. 54, 1441 (1958).

9 R. E. Weston, Jr., Tetrahedron 6, 31 (1959).

10 R. W. Taft, Jr., Steric Effects in Organic Chemistry (Edited by M. S. Newman) Chap. 13. John Wiley, New York (1956).

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DARSTELLUNG VON TETRAAMINO-BENZOCHINON-1,4 AUS FLUORANIL UND CHLORANIL

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Chemisches Laboratorium der Universität Freiburg i.Br.

(Received 5 August 1959)

DURCH Umsetzung von Fluoranil[1] (Tetrafluor-benzochinon-1,4) mit Aminen lassen sich alle vier Halogenatome substituieren, so dass man Aminochinone erhält, die aus anderen Tetrahalogenchinonen nicht zugänglich sind.[2] Im allgemeinen reagieren zwei der Fluoratome sehr rasch, die anderen beiden langsamer oder nur unter energischen Reaktionsbedingungen.

Mit Ammoniak in Benzol oder Äther reagiert Fluoranil bereits bei -70°; in geringer Ausbeute erhält man Diamino-difluor-benzochinon-1,4. Bei höherer Temperatur und grösserer Ammoniakkonzentration verläuft die Reaktion unter Bildung dunkler, nicht kristalliner Produkte, die wahrscheinlich polymer sind.

Tetraamino-benzochinon-1,4 konnten wir jedoch auf anderem Wege darstellen. Umsetzung von Fluoranil mit Phthalimid-kalium in Acetonitril liefert in guter Ausbeute eine gelbe fluorfreie Verbindung, die in allen gebräuchlichen Lösungsmitteln unlöslich ist. Wir schreiben ihr die Konsti-

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[1] K. Wallenfels und W. Draber, Ber. 90, 2819 (1957).

[2] K. Wallenfels und W. Draber, Angew. Chem. 70, 313 (1958).

tution des Tetraphthalimido-benzochinon-1,4 zu. Die gleiche Verbindung erhielten wir in geringerer Ausbeute auch aus Chloranil und Phthalimidkalium. Bei Behandlung mit wässrigem Hydrazin geht sie zunachst in Lösung, dann fallen hellviolette Nädelchen aus, die sich bei leichtem Erwärmen wieder auflosen. Nach einiger Zeit scheidet sich das Tetraamino-chinon in Form bronzeglänzender, fast schwarzer Nadeln ab. Die Verbindung zersetzt sich ab 260°, ist in den gebräuchlichen Lösungsmitteln nur wenig oder beim Erwärmen unter Zersetzung löslich und bildet mit konz. Schwefelsäure ein feinkristallines rotbraunes Sulfat, das 1 Mol H_2SO_4 enthält und in kaltem Wasser nicht hydrolysiert. Die Analyse ergab für $C_6H_8N_4O_2$ (168,16)

C: 42,60 H: 4,89 N: 32,65%

Ber. C: 42,87 H: 4,78 N: 33,31%

IR-Absorptionsbanden (KBr) des freien Chinons bei 1650 und 1670 cm^{-1} (C=O); Sulfat: 1683 cm^{-1} (C=O).

Die neue Verbindung lässt sich reduzieren, acetylieren und reduktiv acetylieren. Die dabei gebildeten Derivate und weitere Reaktionsmöglichkeiten werden zur Zeit untersucht.

Diese Befunde wurden beim International Symposium on Fluorine Chemistry in Birmingham am 18. Juli 1959 mitgeteilt.

Wir danken dem Fonds der Chemischen Industrie für die Unterstützung unserer Arbeiten, der Firma Farbwerke Hoechst AG. für die kostenlose Lieferung von Chemikalien.

A list of papers recently accepted for publication in "Tetrahedron"

R.G. ACKMAN, Sir PATRICK LINSTEAD, B.J. WAKEFIELD and B.C.L. WEEDON: Organic reactions in strong alkalis - I. Fission of ethylenic acids (the Varrentrapp reaction).

R.G. ACKMAN, R.A. DYTHAM, B.J. WAKEFIELD and B.C.L. WEEDON: Organic reactions in strong alkalis - II. Fission of di-ethylenic and acetylenic acids.

R.A. DYTHAM and B.C.L. WEEDON: Organic reactions in strong alkalis - III. Fission of keto- and hydroxy-acids.

W.L. MOSBY and W.L. BERRY: Products of nucleophilic displacement reactions in the anthraquinone series.

J. TROTTER: Bond lengths in benzene derivatives: hybridization or resonance.

G. NATTA and G. MAZZANTI: Organometallic complexes as catalysts in ionic polymerizations.

D.K. BANERJEE, J. DUTTA, A.S. RAO and E.J. JACOB: Synthetic investigation of the building of ring A of steroids.

P.K. GRANT and R. HODGES: The structure of isophyllocladene.

G.A. RUSSELL: Solvent effects in the reactions of free radicals and atoms - VI. Separation of polar and resonance effects in the reactions of chlorine atoms.

E.J. FORBES, M. STACEY, J.C. TATLOW and R.T. WRAGG: The synthesis of 1,2, and 3-trifluoromethylcarbazoles by the Fischer-Indole method.

E.J. FORBES, J.C. TATLOW and R.T. WRAGG: The unequivocal syntheses of 2- and 4-trifluoromethylcarbazoles via diphenyls.

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Tetrahedron Letters No. 14, pp. 1-7, 1959. Pergamon Press Ltd. Printed in Great Britain.

HYDROGEN BONDING IN β-ARYL ETHANOLS

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(Received 10 August 1959)

THE great potential of spectroscopic investigations of hydrogen bonding applied to the solution of configurational and conformational problems in organic chemistry is becoming more widely recognized. As part of a program of research in this field,[1] we have had occasion to examine a large number of nuclear and side-chain substituted β-phenyl ethanols.[2] Very recently, Mateos and Cram[3] have reported spectral observations of a number of diasteriomeric polysubstituted β-phenyl ethanols in the OH region of the infrared. Conclusions concerning the preferred conformations and the steric environments of the hydroxyl group were advanced. It is noteworthy that our interpretations differ from those of the California workers in almost all significant respects. We wish to record a portion of our results and to discuss the reasons for the differences in interpretation.

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* Plastic Laboratory, Princeton University, Princeton, N.J.

1 D. S. Trifan, L. Weinmann and L. P. Kuhn, J. Amer. Chem. Soc. 79, 6566 (1957); P. von R. Schleyer, D. S. Trifan and R. Bacskai, Ibid. 80, 6691 (1958).

2 D. S. Trifan, R. Bacskai, P. von R. Schleyer and C. Wintner, Abstracts, 135th National Meeting of the Amer. Chem. Soc., Boston, Mass., April, 1959, p. 98-O; C. Wintner, A. B. Thesis, Princeton University,(1959).

3 J. L. Mateos and D. J. Cram, J. Amer. Chem. Soc. 81, 2756 (1959).

Since 1936 evidence has been accumulating in the literature[4] that π -electron systems, such as aromatic rings, can function as weak proton acceptor groups in hydrogen bonding. β-Phenyl ethanol itself has been found by several investigators to be intramolecularly hydrogen bonded. Very dilute solutions of this compound in an inert solvent display two concentration independent peaks in the OH stretching region (2.75μ)[1,5] and first overtone region (1.4μ).[6] In their paper, Mateos and Cram did not consider the factor of OH ... π hydrogen bonding.

Our results with β-aryl ethanol, $ArCH_2CH_2OH$, are summarized in Table 1. Listed are the positions of the free peaks, the π -intramolecularly bonded peaks and the ratio of their apparent extinction coefficients. The differences in the two positions, $\Delta\nu$, is taken as a measure of the enthalpy of the hydrogen bond. In addition, the relative proton donor abilities of the various alcohols were determined by ascertaining the position of the intermolecular peak with n-butyl ether as the standard reference proton acceptor.

The effect of nuclear substitution can easily be predicted on theoretical grounds: two effects, working in opposing directions, should be present. For example, a p-nitro group would by its electrical character withdraw electrons from the ring, making it less able to interact with the hydroxyl proton. At the same time, the hydrogen bonding acidity of the side-chain OH group should be enhanced. Electron releasing substituents would

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[4] For literature citations see ref. 1; also, refs. 5,6.

[5] D. Barnard, K. R. Hargrave and G. M. C. Higgins, J. Chem. Soc. 2845 (1956); A. W. Baker and A. T. Shulgin, J. Amer. Chem. Soc. 80, 5358 (1958); H. Kwart and R. T. Keen, Ibid. 81, 943 (1959).

[6] I. M. Goldman and R. O. Crisler, J. Org. Chem. 23, 751 (1958).

TABLE 1[a]. β-Aryl ethanols, $ArCH_2CH_2OH$ (values in cm^{-1})

Aryl group	ν Free	ν Bonded	$\varepsilon f/\varepsilon b$[b]	Δν	Δν to Bu_2O[c]
p-Dimethylamino-phenyl	3631	3595	0.94	36	--
p-Aminophenyl	3633	3598	1.08	35	141
o-Aminophenyl	3632	3600	1.61	32	--
p-Methoxyphenyl	3633	3602	1.26	31	156
Mesityl	3632	3601_5	1.79	30_5	161
2-Naphthyl	3632	3602_5	1.34	29_5	158
1-Naphthyl	3632	3604	1.32	28	159
Phenyl	3631	3604	1.25	27	160
m-Methoxyphenyl	3631	3605	1.17	26	157
p-Chlorophenyl	3632	3612	1.36	20	171
m-Chlorophenyl	3632	3614	1.17	18	172
4-Pyridyl	3632	3619	1.32	13	--
o-Nitrophenyl	3631	3620	1.40	11	181
p-Nitrophenyl	3632	3621_5	1.44	10_5	182
2-Pyridyl[d]	3632	3623	--	9	--
Cyclohexyl	3635	none	--	--	147
1-Cyclohexenyl	3632	3579	1.75	53	149

[a] Perkin-Elmer Model 21 Spectrophotometer, LiF prism. Solutions about 0.005 M in CCl_4. Machine calibrated several times daily against water vapor; the values are corrected averages of several runs and should be accurate to ±1 or 2 cm^{-1}.

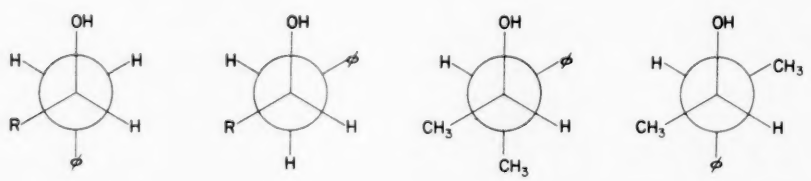
[b] Ratio of the apparent extinction coefficients. Since there is considerable overlap of peaks, these are not very accurate, but can be used for approximate comparisons. These are not measures of the relative fractions of bonded and free molecules because of differences in extinction coefficients.

[c] Probable error: ± 3 cm^{-1}. Solutions about 1 M in Bu_2O.

[d] Intramolecular bonding to N very strong; Δν = 205.

have the opposite effects. In the aromatic carbinols, $ArCH_2OH$, these effects very largely counterbalance each other.[2] The Bu_2O data of Table 1 reveal that the interposition of the additional methylene group in the side chain of the β-aryl ethanols has resulted in a marked reduction, but not a complete elimination, of the second effect. In consequence, the hydrogen bonding basicity of the aromatic ring is the more important factor and marked differences in both the free-bonded $\Delta\nu$ values and their intensity ratios are noted. The $\Delta\nu$ values correlate very well with the Hammett σ constants.

Conformational influences are illustrated by the results with side-chain alkyl substituents (Table 2). α-Substitution decreases the proton donor ability of the OH group, which is known to be in the order primary alcohols> secondary > tertiary.[7] Therefore, $\Delta\nu$ decreases. However, the relative intensity of the bonded peak increases. For steric reasons an increased percentage of molecules are present in the bonding skew conformation II and a decreased percentage in the staggered conformation I, in which intramolecular hydrogen



I II III IV

[7] L. P. Kuhn, J. Amer. Chem. Soc. 74, 2492 (1952).

bonding is not possible. β-Phenyl ethanol itself must exist to an appreciable extent in the skew conformation (II, R=H). The energy of the intramolecular bond, estimated by our temperature studies to be about 1.4 kcal, overcomes the stereo-electric factors which usually favor the staggered arrangement.

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β-Substitution increases both $\Delta\nu$ and the relative intensity of the bonded peak. The latter result is easily explained on conformational grounds similar to the above. Perhaps angle deformation[7] ("Thorpe - Ingold effect") contributes to the former.

The other polysubstituted compounds represent combinations of these effects. The diasteriomeric 3-phenyl-2-butanols, typical of the compounds examined by Mateos and Cram, are worthy of further comment. The $\Delta\nu$ values of the two isomers do not differ significantly, but the free/bonded intensity ratios are strikingly different. In the threo isomer the bonded band is much the stronger of the two, but the erythro compound displays a more intense free peak. Conformation III, with the phenyl and the OH in a skew relationship, is of major importance with the threo isomer, but the staggered rotomer, IV, must be more favorable for the erythro material.

Using a spectrometer equipped only with a low resolution NaCl prism, not capable of resolving the details of the intramolecular hydrogen bonding (discussed above), Mateos and Cram examined the intermolecular (OH...O type) dimerization of their alcohols. The threo isomer had a less intense dimer peak than the erythro, but both absorbed at about the same position. The intensity relationships of the so-called "free" peaks were in the reverse order with

TABLE 2. Effect of side chain substitution in β-phenyl ethanols (cm^{-1})

Substituents	ν Free	ν Bonded	$\varepsilon f/\varepsilon b$	$\Delta\nu$	$\Delta\nu$ to Bu_2O
None	3631	3604	1.25	27	160
α-Methyl	3622_5	3602	0.81	20_5	146
α-t-Butyl	3631	3605	0.52	26	149
α,α-Dimethyl	3611	3594	0.94	17	133
β-Methyl	3636	3603	0.98	33	155
β-Ethyl	3635	3601	0.86	34	162
β,β-Dimethyl	3639	3601	0.86	38	161
α,β-Dimethyl-threo	3622	3595	0.45	27	145
α,β-Dimethyl-erythro	3629	3602	1.50	27	151
α,α,β-Trimethyl	3614	3591	0.89	23	127
α,α,β,β-Tetramethyl	3619	3593	0.70	26	136
trans-2-Phenylcyclohexanol-1	3621w	3598	0.23	23	147

the threo isomer appearing to absorb at very much lower frequencies. Both the apparently lower $\Delta\nu$ (dimer) and the smaller amount of dimerization of the threo compounds were explained on the presumption of a more hindered average environment of the hydroxyl group.

A more convincing explanation of these results is as follows. The threo isomer is much more highly intramolecularly bonded. The "free" peak observed by Mateos and Cram for this compound is in reality predominantly the intramolecularly π-bonded peak. In actual fact the positions of the free peaks for the two diasteriomers are not very different, and the $\Delta\nu$ -dimer values are quite comparable (dimer positions: threo, 3496; erythro, 3498). Steric effects, therefore, are not influencing appreciably the strength ($\Delta\nu$) of the intermolecular hydrogen bonds in these compounds. While more hindered alco-

hols in general do form a smaller percentage of dimer, it seems likely that the less intense dimer peak of the threo isomer is due principally to competitive intramolecular bonding. Similar reinterpretations are necessary for the other diasteriomeric pairs reported by Mateos and Cram. It is clear that the factor of OH...π hydrogen bonding must be taken into account in interpreting the NMR and other physical properties of these compounds. Such hydrogen bonding contributes importantly to the energy relationships of the possible conformations of molecules.

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The points raised here will be elaborated and the effects of polyphenyl substitution and incorporation of these functional groups in cyclic systems will be described in forthcoming publications. We have noted similar effects in the spectra of alcohols possessing other proton accepting functional groups.

Acknowledgement - We are grateful to Mr. Lewis Robinson for redetermining the spectra of all of the compounds.

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THE STRUCTURE OF JULOCROTINE

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(Received 14 August 1959)

ANASTASI[1] has reported the isolation of an alkaloid "julocrotine" from Julocroton montevidensis (fam. Euphorbiaceae), but except for the observation that it gives the usual alkaloid reactions, is labile to acid or alkali, melts at 105° and corresponds to the empirical formula $C_{19}H_{26}N_2O_3$, no further information has been published on this substance. We should now like to report certain experiments which demonstrate that julocrotine possesses structure I.

In our hands, julocrotine exhibited m.p. 108-109°, $[\alpha]_D$ -9° (chloroform), -50° (methanol) and its empirical formula corresponded to $C_{18}H_{24}N_2O_3$

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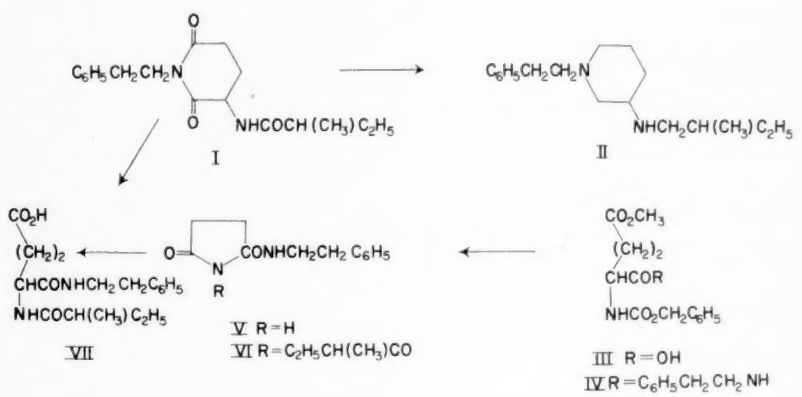
* Present address: Department of Chemistry, Stanford University, Stanford, California.

[1] C. Anastasi, Anal. Asoc. Quim. Argentina 13, 348 (1925). Subsequently the substance was also isolated from J. subpannosus and J. camporum (unpublished results of A. Novelli cited by A. Novelli and O. O. Orazi, Rev. Farmaceutica (Buenos Aires) 92, 102 (1950)).

(Calc.: C, 68.33; H, 7.65; N, 8.85; O, 15.17; C-CH_3, 4.75; mol. wt., 316. Found: C, 68.09; H, 7.72; N, 9.03; O, 15.41; OCH_3, 0.0; C-CH_3, 6.11; M (Rast), 309). In the strict sense of the word, julocrotine is not an alkaloid since it does not possess any titratable basic nitrogen. Its ultraviolet absorption spectrum is typical of an isolated benzene ring, while its infrared spectrum (chloroform) exhibited bands at 2.93 (sharp), 5.76 (w), 5.93 (s) and 6.65 (s) μ. Perhydrogenation with platinum oxide in acetic acid resulted in the uptake of three molar equivalents of hydrogen and the formation of hexahydrojulocrotine ($C_{18}H_{30}N_2O_3$, m.p. 93-94°), which does not anymore show the typical ultraviolet benzenoid absorption.



Reduction of julocrotine with lithium aluminum hydride caused the loss of all oxygen functions and yielded an oily base ($[\alpha]_D$ -12.6° (chloroform); Calc. for $C_{18}H_{30}N_2$: C, 78.77; H, 11.02; N, 10.21; C-CH_3, 5.48. Found: C, 78.10; H, 10.92; N, 9.84; C-CH_3, 8.10), subsequently shown to be II. In contrast to the non-basic starting material julocrotine, the lithium

aluminum hydride reduction product formed a dipicrate (m.p. 186-187°) and a dimethiodide (m.p. 226-227°) thus suggesting that the three oxygen atoms of julocrotine are present in the form of an amide and an imide function. Hydrogenation of the liquied base again resulted in the uptake of three molar equivalents of hydrogen and the disappearance of the benzenoid absorption spectrum, implying that julocrotine must contain one additional ring aside from a benzene nucleus. Hofmann degradation of the dimethiodide of m.p. 226-227° yielded an optically active diamine (to be described in our detailed publication) and a neutral oil, which furnished benzoic acid upon permanganate oxidation. Further information about the benzene fragment was provided by the alkaline hydrolysis of julocrotine, from which β-phenylethylamine could be isolated. In addition, there were isolated two isomeric acids (corresponding to $C_{18}H_{26}N_2O_4$) containing no basic nitrogen and these are referred to as julocrotic acid-A (m.p. 119-122°, $[\alpha]_D$ +14° (methanol); methyl ester $C_{19}H_{28}N_2O_4$, m.p. 148-149°) and julocrotic acid-B (m.p. 133.5-135°). These results are best interpreted by assuming alternate hydrolytic opening of an unsymmetrical cyclic imide.

Comparison of the infrared carbonyl bands of julocrotine ($\lambda_{max}^{CHCl_3}$ 5.76 (w) and 5.93 (s) μ) with those of N-β-phenylethylsuccinimide ($\lambda_{max}^{CHCl_3}$ 5.63 (w) and 5.85 (s) μ) and N-β-phenylethylglutarimide ($\lambda_{max}^{CHCl_3}$ 5.78 (w) and 5.96 (s) μ) demonstrates clearly[2] that julocrotine is a glutarimide derivative. This was established by the course of the acid hydrolysis (dioxanehydrochloric acid, 24 hr refluxing) which furnished β-phenyl-

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[2] Infrared bands for other substituted succinimides and glutarimides are given by H. K. Hall and R. Zbinden, J. Amer. Chem. Soc. 80, 6428 (1958) and by V. M. Clark, A. W. Johnson, I. O. Sutherland and A. Todd, J. Chem. Soc. 3283 (1958).

ethylamine, L-(+)-glutamic acid and (+)-α-methylbutyric acid [p-bromoanilide, m.p. 135-136°, $[\alpha]_D$ +31.3° (acetone); anilide, m.p. 96-97°, $[\alpha]_D$ +40.2° (acetone)], all of which can be accommodated in expression I for julocrotine.

Verification of this structure was provided by the synthesis of julocrotic acid-A (VII) according to the following scheme. γ-Methyl N-carbobenzyloxy-L-glutamate (III)[3] was converted to the acid chloride with phosphorus pentachloride in ether solution and treated directly with β-phenylethylamine to afford the amide IV (m.p. 124-125°, $[\alpha]_D$ -8.6° (chloroform), $\lambda_{max}^{CHCl_3}$ 2.92, 5.75 and 5.93 μ; Calc. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03; O, 20.08. Found: C, 66.15; H, 6.36; N, 7.29; O, 20.11). Hydrogenolysis with palladium black in aqueous methanol containing some acetic acid, evaporation to dryness and recrystallization from ether gave the β-phenylethylamide of 2-keto-pyrrolidine-5-carboxylic acid (V) (m.p. 140-142°, $[\alpha]_D$ -47° (chloroform); Calc. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78. Found: C, 66.84; H, 6.86; N, 11.98; O, 14.03; OCH_3, 0.0), identical with a specimen derived from successive treatment of 2-ketopyrrolidine-5-carboxylic acid[4] with thionyl chloride and then with β-phenylamine. Treatment of V with (+)-α-methylbutyryl chloride in pyridine solution led to N-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (VI) (m.p. 102-104°, $[\alpha]_D$ -24° (methanol); Calc. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.12; H, 7.45; N, 8.92), which was hydrolyzed[5] with 5% methanolic

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[3] W. E. Hanby, S. G. Waley and J. Watson, J. Chem. Soc. 3239 (1958).

[4] E. Abderhalden and K. Kautzsch, Z. Physiol. Chem. 68, 487 (1910).

[5] See A. R. Battersby and J. C. Robinson, J. Chem. Soc. 2076 (1956).

potassium hydroxide to julocrotic acid-A (VII). Identity with a specimen derived from julocrotine (I) was established by coincidence of the melting points, optical rotations and infrared spectra of the appropriate acids and methyl esters.

The work at Wayne State University was supported by grant No. H-2574 from the National Heart Institute, National Institutes of Health, U.S. Public Health Service. One of us (T.N.) is the recipient of a Fulbright Travel Grant while on leave of absence from the University of Kyoto.

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THE CONFORMATION OF 2-FLUOROCYCLOHEXANONE

Andrew S. Kende

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1959

(Received 19 August 1959)

IN connection with studies on the Favorskii rearrangement we have prepared 2-fluorocyclohexanone (I) in 40 per cent yield by reaction of the sodium salt of 2-hydroxymethylenecyclohexanone with perchloryl fluoride in ethanol.[1] Fluorination is accompanied by loss of the formyl group and leads directly to I, b.p. 76-77°/17 mm, n_D^{25} = 1.4390 (Found: C, 61.74; H, 7.81; F, 15.96). The conformation of this simple α-haloketone is of interest since it provides a test for the hypothesis[2] that conformational equilibria in cyclic α-haloketones are controlled largely by (1) electrostatic dipole-dipole repulsions which destabilize equatorial halogen, and (2) steric 1,3-diaxial interactions, of particular importance in the case of large axial ring substituents, which destabilize the axial conformer. Calculation of the electrostatic effect using the mathematical model of Allinger and Allinger[3]

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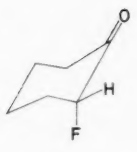
[1] Inman, Oesterling and Tyczkowski, J. Amer. Chem. Soc. 80, 6533 (1958). An independent synthesis of I has been achieved by W. S. Johnson and V.J. Bauer, University of Wisconsin (Private communication).

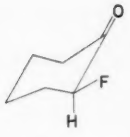
[2] Corey, J. Amer. Chem. Soc. 75, 2301 (1953). Predominance of the "chair" form is assumed cf. [Nace and Turner, Ibid. 75, 4063 (1953)].

[3] Allinger and Allinger, Tetrahedron 2, 64 (1958). The value 1.40 Å for for the C-F bond length and the limits 1.40-1.80 for thé C-F bond moment were employed in the present calculations.

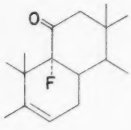
leads to an energy difference favoring Ia over Ie by 2.1 ± 0.3 kcal/mole. Since fluorine is only slightly larger than hydrogen[4] the steric effect in favor of Ie should not exceed 0.5 kcal/mole,[2] so that the net predominance of the axial conformation Ia by a factor of about 10 would be predicted.



Ia



Ie



II

In chloroform solution the fluoroketone I exhibits a single carbonyl peak at 5.78μ (in CCl_4, at 5.74 μ). The ultraviolet spectrum of I has λ_{max}^{EtOH} = 283 mμ, ε = 17.5 (in cyclohexane, λ_{max} = 294 mμ, ε = 17.7). Comparison of these data with the values observed[5] for the axially-fluorinated 9α-fluoro-11-ketosteroid grouping II, $\lambda_{CO}^{CHCl_3}$ = 5.83 μ and $\lambda_{max}^{EtOH-CHCl_3}$ = 310 mμ, (ε = 41), and with the well established conformational correlations in the infrared[6] and ultraviolet[7] spectra of cyclic α-chloro-

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[4] Pauling, Nature of the Chemical Bond pp. 164, 189-191, Cornell University Press, Ithaca (1948). Van der Waals radii given are: F, 1.35; H, 1.2 Å.

[5] Kende and Allen, unpublished observations.

and α-bromoketones strongly suggests that 2-fluorocyclohexanone exists mainly as Ie. This assignment was supported by a determination of the dipole moment of I in benzene solution at 35°.[8] The experimental value, 3.86 ± 0.10 D, is in reasonable agreement with the calculated[3] value for Ie (4.0 ± 0.2 D) and precludes any substantial percentage of conformer Ia (2.7 ± 0.2 D) under these conditions.

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Clearly the published[2,3] semiquantitative treatment of the α-haloketone problem leads to a prediction strikingly at variance with the experimental data in this and in related systems.[9] A further anomaly arises from the observation that spectra of 21-fluoropregnenolone[10] (III) in dioxane or chloroform solutions of varying concentrations possess two distinct carbonyl peaks, near 5.78 and 5.83 μ, the former somewhat more intense. Since such splitting is not observed in solid state spectra of III it may be attributed to the presence of two principal types of rotamers, possibly IIIa and IIIb, of which the former appears to predominate despite increased dipole repulsions.[11]

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[6] Jones, Ramsay, Herling and Dobriner, J. Amer. Chem. Soc. 74, 2828 (1952).

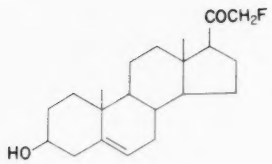
[7] Cookson, J. Chem. Soc. 282 (1954); see also ref. 9.

[8] The author is indebted to R. J. Best (Research Division, American Cyanamid Co., Stamford, Conn.) for the dipole moment measurements, which were carried out by the technique of Halverstadt and Kumler, J. Amer. Chem. Soc. 64, 2988 (1942).

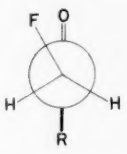
[9] E.g., 2-fluorocholestan-3-one, for which the (equatorial) 2α configuration was inferred by Gabbard and Jensen [J. Org. Chem. 23, 1406 (1958)] and Djerassi, Fornaguera and Mancera [J. Amer. Chem. Soc. 81, 2383 (1959)] on the basis of spectroscopic and rotatory dispersion data.

[10] Tannhauser, Pratt and Jensen, J. Amer. Chem. Soc. 78, 2658 (1956).

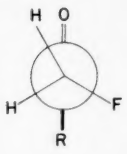
[11] Entirely comparable phenomena have been observed for chloroacetone



III



IIIa



IIIb

The factors contributing to the observed stabilities of electrostatically unfavorable conformers are difficult to evaluate. It is likely that a dipole-solvent interaction of the type studied by Powling and Bernstein[12] effects a substantial decrease in the electrostatic energy term for the more polar isomer. In addition, the possible operation of a stereospecific hyperconjugation effect involving that component of each α C-H sigma bond which is perpendicular to the C-C-O plane could provide optimum stabilization to those conformers (such as Ie and IIIa) having the C-F bond very nearly within the C-C-O plane.[13]

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and for a number of α-chloroacetophenones by Bellamy, Thomas and Williams, J. Chem. Soc. 3704 (1956); 4294 (1957).

12 Powling and Bernstein, J. Amer. Chem. Soc. 73, 1815 (1953).

13 Evidence in favor of hyperconjugative stabilization of carbonyl compounds by α C-H bonds has been presented by Baddeley and Gordon, J. Chem. Soc. 2190 (1952); and by Taft and Kreevoy, J. Amer. Chem. Soc. 79, 4011 (1957).

Tetrahedron Letters No. 14, pp. 17-20, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE ANOMALOUS CHLORINATION OF ESTRADIOL 17β-ACETATE WITH ISOCYANURIC CHLORIDE

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1959

(Received 14 August 1959)

INTRODUCTION of halogen atoms at various positions of the steroid molecules has often given rise to interesting biological properties.

Now, the author wishes to report the synthesis of 2,4,10β-trichloro-17β-acetoxy-1,4-estradiene-3-one and 10β-chloro-17β-acetoxy-1,4-estradiene-3-one by a novel reaction. Chlorination of estradiol 17β-acetate (I) with isocyanuric chloride[1] in t-butyl alcohol-acetic acid gave a mixture which afforded by fractional crystallization 2,4,10β-trichloro-17β-acetoxy-1,4-estradiene-3-one (II), m.p. 205°, $[\alpha]_D^{17}$ +1.9 (c 1.3, $CHCl_3$), (Found: C, 57.67; H, 5.46; Cl, 24.13 Calc. for $C_{20}H_{23}O_3Cl_3$: C, 57.60; H, 5.56; Cl, 25.51) and 10β-chloro-17β-acetoxy-1,4-estradiene-3-one (III), m.p. 124°, $[\alpha]_D^{18}$ + 10.7 (c 1.0, $CHCl_3$), (Found: C, 68.28; H, 7.22; Cl, 9.90. Calc. for $C_{20}H_{25}O_3Cl$: C, 69.02; H, 7.24; Cl, 10.19).
The structure of II was based on its infrared absorption at 6.20 μ (1,4-diene-3-one)[2] and ultraviolet absorption maximum at 258 mμ (E 15.400).

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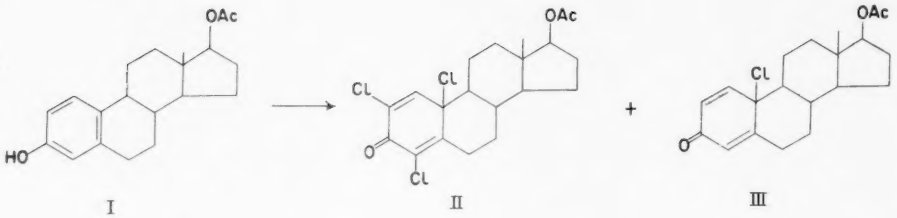
[1] F. Mukawa, J. Chem. Soc. Japan 78, 450 (1957).

[2] N. Jones and F. Herling, J. Org. Chem. 19, 1252 (1954).



I II III

The orientation of 10β-chlorine atom was supported by the fact that the rotatory dispersion curve of II was nearly identical with 4-chlorotestosterone.[3] (Fig. 1).

The ultraviolet spectrum of II in ethanolic alkaline solution[4] showed a maximum at 300 mμ, which is typical for the 3-hydroxyestra-1,3,5(10)-triene system.[5] Reduction of II with zinc and acetic acid gave I, similarly, reduction with sodium borohydride in methanol gave 2(or 4)-chloro-estradiol 17β-acetate (IV), m.p. 235° (dec.), $\lambda_{max}^{dioxane}$ 282 mμ (E 2,300),[6] infrared: λ_{max} 2.9(s), 5.9(v.s), 7.7(m), 7.9(m),

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[3] C. Djerassi, Private communication. (1958); C. Djerassi, R. Rimiker and B. Rimiker, J. Amer. Chem. Soc. 78 6362, 6377 (1956).

[4] A. S. Meyer, J. Org. Chem. 20, 1240 (1955).

[5] L. Dorfman, Chem. Rev. 53, 47 (1953).

[6] 2,4-Dibromoestradiol [R. B. Woodward, J. Amer. Chem. Soc. 62, 1625 (1940)] has a maximum at 293 mμ (E 3,300, dioxane) in the ultraviolet region.

1959

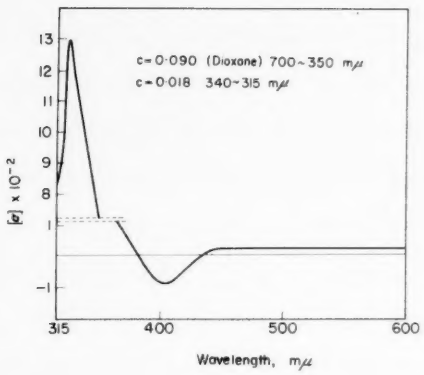


FIG. 1.

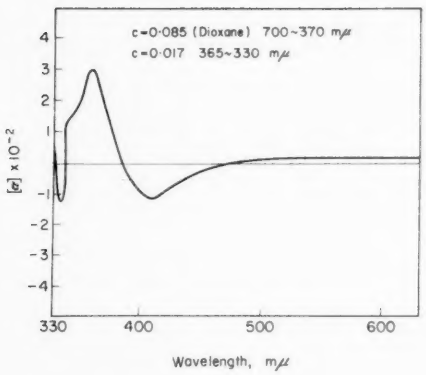


FIG. 2.

9.2(w), 9.6(w), 9.9(w), 11.6(w), 12.8(m)μ, (Found: C, 68.80; H, 7.51; Cl, 10.30. Calc. for $C_{20}H_{25}O_3Cl$: C, 69.02; H, 7.24; Cl, 10.19). The monochloride (III) was readily transformed into I in alkaline solution. The reduction of III with sodium borohydride in methanol or the hydrogenation of II in the presence of palladium catalyst also gave I. The presence of the 1,4-diene-3-one system was revealed by its ultraviolet spectrum (λ_{max}^{EtOH} 248 mμ, E 16,000) and infrared absorption spectra (band at 6.20 μ). The β-orientation of chlorine atom was supported by the fact that the shape of the rotatory dispersion curve roughly coincided with that of cholest-1,4-diene-3-one type. (Fig. 2).[3] Thus the structure of III is elucidated as 10β-chloro-17β-acetoxy-1,4-estradiene-3-one. Bioassay: II showed estrogenic action when tested with adult ovariectomized mice (Allen - Doisy virginal smear method), and a slight androgenic activity with castrate immature rats. III showed estrogenic action with duration.

Acknowledgements - The author is indebted to Mr. M. Sawai of this laboratory for his helpful discussion and to Mr. O. Kobayashi of Teikoku Hormone Manufacturing Co. for the biological data.
Thanks are also due to Prof. C. Djerassi (Wayne State University) for the measurment of the rotatory dispersion and his kind advice.

Tetrahedron Letters No. 14, pp. 21-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

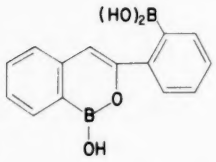
AROMATIC BORON-OXYGEN HETEROCYCLES

M.J.S. Dewar and R. Dietz

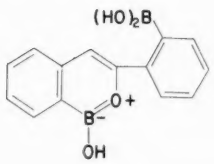
Department of Chemistry, Queen Mary College, Mile End Road, London

(Received 25 August 1959)

LETSINGER and NAZY[1] recently reported the isomerization of 2:2'-tolandiboronic acid to a compound of doubtful structure. We favour the formation I.



I



II

Its unusual properties are then attributable to the contribution of the pseudoaromatic structure II. The recently proposed[2] system of nomenclature

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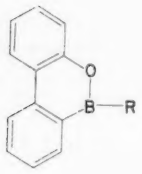
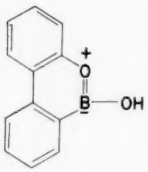
[1] Letsinger and Nazy, J. Amer. Chem. Soc. 81, 3013 (1959).

[2] Dewar and Dietz, J. Chem. Soc. In press.

would accommodate this as a derivative of 1:2-boroxaronaphthalene. This representation is supported by our synthesis of an analogous heteroaromatic system.



III



IV

Successive reaction of 2-hydroxydiphenyl with boron trichloride at -70°, and aluminium chloride in benzene at 60° gave 10-chloro-10:9-horoxarophenanthrene (III, R=Cl) (Found: Cl, 15.8; B, 4.8%. $C_{12}H_8OBCl$ requires Cl, 16.6; B, 5.1%). Hydrolysis was rapid and gave 10-hydroxy-10:9-boroxarophenanthrene (III, R=OH), characterized as the anhydride, m.p. 205-206.5°. (Found: C, 76.5; H, 4.3; B, 5.4%, neutralization equivalent 184. $C_{24}O_{16}O_3B_2$ requires: C, 76.6; H, 4.3; B, 5.8%, neutralization equivalent 187). Crystallization from methanol gave the methyl ester (III, R=OMe), m.p. 63.5-64.5 (Found: C, 74.3; H, 5.3%. M,197. $C_{13}H_{11}O_2B$ requires C, 74.3; H, 5.3; M, 210), and reaction of the chloro-compound with phenyl magnesium bromide gave 10-phenyl-10:9-boroxarophenanthrene (III, R=Ph), m.p. 82-3° (Found: C, 84.3; H, 5.1; B, 3.9%, M, 249. $C_{18}H_{13}OB$ requires

C, 84.4; H, 5.1; B, 4.3%, M, 256). Some bromo derivatives have also been prepared.

Evidence for these structures include the methods of preparation, and the ultra-violet spectra, which are quite different from those of substituted diphenyls, rather resembling those of the corresponding 10:9-borazarophenanthrenes.[3]

1959

10-Hydroxy-10:9-boroxarophenanthrene, although classically an internal ester of 1-(1-hydroxyphenyl)-phenyl boronic acid (III, R=OH), has considerable stability to aqueous acid and alkali, in which the ultra-violet spectrum is unchanged, and to oxidation. We attribute this stability to its aromatic nature, emphasized by IV.

Full details of this work will appear shortly.

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[3] Dewar, Kubba and Pettit, J. Chem. Soc. 3073 (1958).

Tetrahedron Letters No. 14, pp. 24-28, 1959. Pergamon Press Ltd. Printed in Great Britain.

CONSTITUTION OF CAROTOL AND DAUCOL

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Department of Natural Products, Institute of Chemistry,

Czechoslovak Academy of Science, Prague

(Received 11 September 1959)

SEVERAL years ago, we, in these Laboratories, studied the sesquiterpenic alcohol carotol[1] of molecular formula $C_{15}H_{26}O$ and ascribed, on the basis of dehydrogenation which afforded 1,7-dimethyl-4-isopropylnaphtalene (II) as the main product, the carbon skeleton I to it. As the dehydrogenation was carried out in the presence of palladized charcoal under relatively drastic conditions and as it gave rise to the formation of a certain amount of azulenes which was not in accordance with the proposed formula for carotol, we re-investigated this sesquiterpenic alcohol.

On sulphur dehydrogenation, neither carotol nor the unsaturated hydrocarbon prepared by dehydration of dihydrocarotol afforded the naphtalenic hydrocarbon II but only a small amount of a mixture of azulenes. As the aromatization of hydrogenated naphtalenic systems usually proceeds without difficulties, the negative result, in our case, was contradictory

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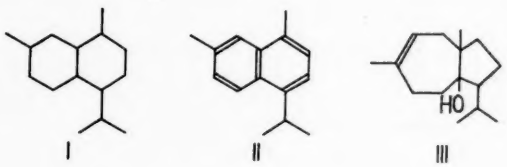
[1] F. Šorm and L. Urbanek, Coll. Czech. Chem. Comm. 13, 49, 420 (1948).

to the isocadalene skeleton of carotol; the formation of II, on the other hand, was due obviously to the isomerization in the course of the reaction with palladized charcoal. On the basis of degradation reactions, we arrived at formula III for carotol; the correctness of this formula was verified, above all, by two independent proofs of the existence of a seven-membered ring in the molecule of carotol.

1959



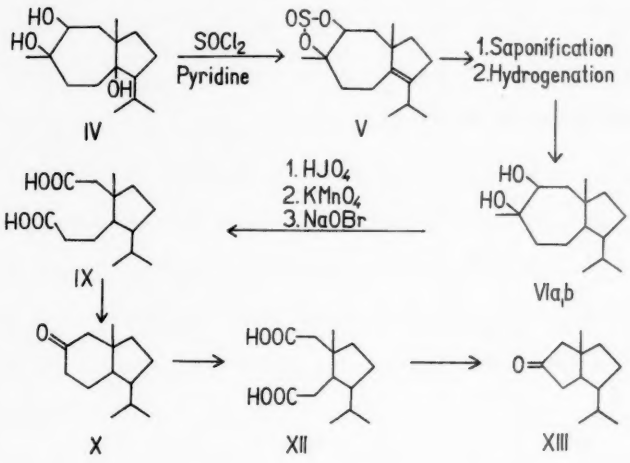
I II III

On treatment with thionyl chloride in pyridine, the triol[1] IV afforded an unsaturated cyclic sulphite (V) which on subsequent hydrolysis and hydrogenation yielded a mixture of two crystalline stereoisomeric diols (VI a, b,) (m.p. 116-117° and 91.5-93°; Found: C, 74.69; H, 11.57; C, 75.03; H, 11.89. $C_{15}H_{28}O_2$ requires: C, 74.95; H, 11.74). On oxidation with periodic acid, the diol VIb afforded the keto-aldehyde VII, which on further oxidation with potassium permanganate in acetic acid yielded keto-acid VIII. The latter, on treatment with hypobromite, was converted into dicarboxylic acid IX. Pyrolysis of its barium salt afforded ketone X (I.R. max. 1717 cm^{-1}, semicarbazone m.p. 184-186°; Found: C, 66.63; H, 9.96; N, 16.83. $C_{14}H_{25}N_3O$ requires: C, 66.89; H, 10.03; N, 16.72).

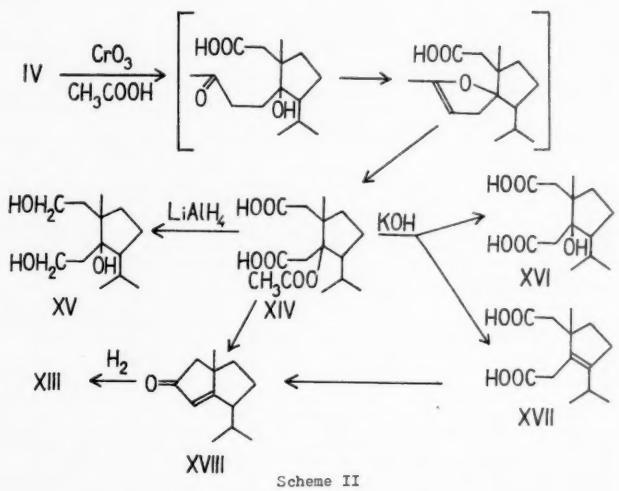
Its monobenzylidene derivative XI when ozonized yielded dicarboxylic acid XII (dimethyl ester b.p. (bath temperature) 128-135°/0.3 mm; Found: C, 66.38; H, 9.48. $C_{15}H_{26}O_4$ requires: C, 66.63; H, 9.69), which on pyrolysis of its barium salt again converted into a ketone XIII (I.R. max. 1741 cm^{-1}, semicarbazone m.p. 197.5-199°. Found: C, 65.52; H, 10.03; N, 17.89. $C_{13}H_{23}N_3O$ requires: C, 65.78; H, 9.77; N, 17.71). All these reactions are outlined in Scheme I.

On treatment with chromic acid in acetic acid, the triol IV afforded acetoxydicarboxylic acid XIV as the main product (I.R. max. 1708 cm^{-1}, 1735 cm^{-1}; m.p. 169-172°; Found: C, 60.01; H, 8.16. $C_{15}H_{24}O_6$ requires: C, 59.98; H, 8.05; dimethyl ester b.p. (bath temperature) 155-160°/0.06 mm; Found: C, 62.17; H, 8.61. $C_{17}H_{28}O_6$ requires: C, 62.17; H, 8.59). The presence in the acid XIV of an acetoxy group was verified, besides the infra-red spectrum, by the course of pyrolysis of XIV which affords acetic acid in almost quantitative yield, further by the reduction with lithium aluminium hydride which leads to the triol XV (b.p. (bath temperature) 175-190°/0.1 mm; Found: C, 67.54; H, 11.38; 1.42 H act. $C_{13}H_{26}O_3$ requires: C, 67.78; H, 11.38; H act. 1.31) and finally by alkaline hydrolysis which affords, besides acetic acid, hydroxydicarboxylic acid XVI (m.p. 147°; Found: C, 60.31; H, 8.77; $C_{13}H_{22}O_5$ requires: C, 60.44; H, 8.59) and the unsaturated dicarboxylic acid XVII (dimethyl ester b.p. (bath temperature) 140°/0.3 mm; Found: C, 66.91; H, 9.01. $C_{15}H_{24}O_4$ requires: C, 67.13; H, 9.02. Pyrolysis of the barium salt of XVII or better directly of the acid XIV gave rise to the ketone XVIII (I.R. max. 1715 cm^{-1}, 1623 cm^{-1}) which on hydrogenation afforded a ketone (I.R. max. 1742 cm^{-1}); its semicarbazone (m.p. 199-200°; Found: C, 65.55; H, 9.98;

N, 17.58; $C_{13}H_{23}N_3O$ requires: C, 65.78; H, 9.77; N, 17.71) according to the mixed melting point appeared to be identical with the semicarbazone of XIII. All these reactions are outlined in Scheme II.



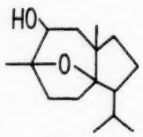
Scheme I



Scheme II

On treatment with nitric acid, the triol IV yielded, besides other products, also isobutyric and succinic acid. These findings together with the above mentioned course of alkaline hydrolysis of the acid XIV corroborate the position of functional groups in carotol in the course of formula III.

The alcohol daucol[2] (XIX) from the oil of Daucus carota L. seeds which was prepared also from carotol on oxidation with peracids[3] or from IV on treatment with benzoic anhydride as well was considered to be the epoxide of carotol. As daucol may be oxidized by means of chromic acid in pyridine to the keto-ether XX (I.R. max. 1719 cm^{-1} m.p. 44-45°; Found: C, 76.56; H, 10.41. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24) it evidently is not an epoxide but a hydroxy-ether of formula XIX.



XIX

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[2] E. Richter, Arch. Pharm. 247, 391 (1909).

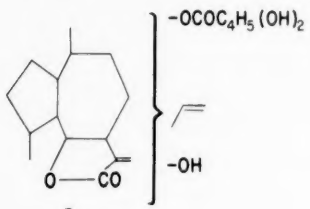
[3] Y. Asahina and T. Tsukamoto, J. Pharm. Soc. Japan 525, 961 (1925); Chem. Abstr. 20, 284 (1926).

1959

E R R A T U M

M. Suchý, V. Benešová, V. Herout and F. Šorm: Contribution on the structure of cnicin, the bitter principle from Cnicus Benedictus L., Tetrahedron Letters No. 10, pp. 5-9 (1959).

Due to an oversight, the lactone group in formula I on p. 7 of the above article was omitted. The correct formula I is reproduced below.



I

A list of papers recently accepted for publication in "Tetrahedron"

R.G. ACKMAN, Sir PATRICK LINSTEAD, B.J. WAKEFIELD and B.C.L. WEEDON: Organic reactions in strong alkalis - I. Fission of ethylenic acids (the Varrentrapp reaction).

R.G. ACKMAN, R.A. DYTHAM, B.J. WAKEFIELD and B.C.L. WEEDON: Organic reactions in strong alkalis - II. Fission of di-ethylenic and acetylenic acids.

R.A. DYTHAM and B.C.L. WEEDON: Organic reactions in strong alkalis - III. Fission of keto- and hydroxy-acids.

W.L. MOSBY and W.L. BERRY: Products of nucleophilic displacement reactions in the anthraquinone series.

J. TROTTER: Bond lengths in benzene derivatives: hybridization or resonance.

G. NATTA and G. MAZZANTI: Organometallic complexes as catalysts in ionic polymerizations.

D.K. BANERJEE, J. DUTTA, A.S. RAO and E.J. JACOB: Synthetic investigation of the building of ring A of steroids.

P.K. GRANT and R. HODGES: The structure of isophyllocladene.

G.A. RUSSELL: Solvent effects in the reactions of free radicals and atoms - VI. Separation of polar and resonance effects in the reactions of chlorine atoms.

E.J. FORBES, M. STACEY, J.C. TATLOW and R.T. WRAGG: The synthesis of 1,2, and 3-trifluoromethylcarbazoles by the Fischer-Indole method.

E.J. FORBES, J.C. TATLOW and R.T. WRAGG: The unequivocal syntheses of 2- and 4-trifluoromethylcarbazoles via diphenyls.

E.J. FORBES and R.T. WRAGG: The syntheses of 2-, and 4-trifluoromethyl carbazoles via diphenylamines.

E. NIELD and J.C. TATLOW: Polyfluoro-aromatic compounds - III. Tetra- and tri-fluoro-p-benzoquinone.

K.W. GOPINATH, T.R. GOVINDACHARI and U. RAMADAS RAO: The alkaloids of Zanthoxylum rhetsa DC.

K.W. GOPINATH, T.R. GOVINDACHARI and S. RAJAPPA: Synthesis of calycanine.

1959

19

Tetrahedron Letters No. 15, pp.1-4, 1959. Pergamon Press Ltd., Printed in Great Britain.

1959

ON THE STEREOCHEMISTRY OF COLUMBIN

M. P. Cava, B. Weinstein and S. S. Malhotra

McPherson Chemical Laboratory, The Ohio State University

Columbus 10, Ohio

(Received 3 August 1959)

THE elucidation of the structure of columbin (I) by Barton and Elad revealed that this diterpene possessed a rearranged sclareol skeleton; the reasonable suggestion was made that columbin may be regarded as derived from a normal diterpene precursor by appropriate methyl migrations which might have stereochemical implications.[1]

In view of our earlier interest in the columbin problem,[2] we wish to record our speculations concerning the stereochemistry of columbin as developed from the observed rotatory dispersion curve of octahydrodecarboxycolumbic acid (II).[1,2]

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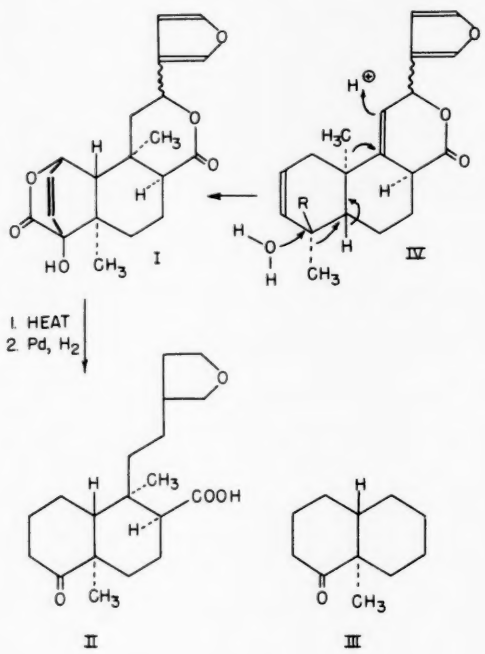
[1] D. H. R. Barton and D. Elad, J. Chem. Soc. 2085, 2090 (1956).

[2] M. P. Cava and E. J. Soboczenski, J. Amer. Chem. Soc. 78, 5317 (1956).



The observed R.D. values of the acid II in methanol (ca. 0.10) are: $[\alpha]_{320}$ + 470°, max $[\alpha]_{310}$ + 1440°, min $[\alpha]_{305}$ + 940°, max $[\alpha]_{320.5}$ + 1240°, min $[\alpha]_{270}$ - 1860°. These values, corrected for solvent effect (+ 7.5 for dioxane),[3] are very close to those recorded for the simple

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[3] C. Djerassi, R. Riniker and B. Riniker, J. Amer. Chem. Soc. 78, 6377 (1956).

bicyclic model,[4] (+)-trans-9-methyldecalone-1 (III). This correlation establishes the absolute stereochemistry of the angular methyl group at the A/B ring fusion in the acid II, and also in columbin itself. The trans decalin junction is not rigorously proved by the above data, but is very likely on biogenetic grounds.

1959

The shift of methyl groups postulated by Barton[1] to occur in the biogenesis of columbin from its hypothetical precursor of the general type IV recalls the biogenesis of friedelin from β-amyrin,[5] in which a concerted all-axial migration takes place. If a similar concerted shift occurs in the biogenesis of columbin, then the configuration of the second angular methyl group of columbin must necessarily be axial, i.e. alpha. The very ready base catalyzed isomerization of columbin to isocolumbin involves only an epimerization of the active hydrogen of the saturated lactone system.[1] It follows from these considerations that in the conversion of the lactone from cis to trans, an axial lactone carbonyl is being epimerized to the more stable equatorial position. This conformational change explains the remarkable shift of the lactone carbonyl frequency from 5.80 μ to 5.73 μ which occurs on passing from columbin to isocolumbin.[6]

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[4] C. Djerassi, R. Riniker and B. Riniker, J. Amer. Chem. Soc. 78, 6362 (1956).

[5] E. J. Corey and J. J. Ursprung, J. Amer. Chem. Soc. 77, 3668 (1955).

[6] The value of 5.80 μ was previously assigned to a β-γ-unsaturated lactone (cf. Ref. 2).

Concerning the unsaturated lactone ring: the observation that this lactone system does not open easily with base supports the placing of the ester bridge on the same side as the angular methyl group (carbonyl hindrance). The ethylenic bridge, which is readily reduced, is placed on the other, less hindered side of the molecule.

The absolute configuration of the β-furyl group cannot be surmised from the evidence now at hand.

Not the least interesting conclusion of the arguments presented here is that the hypothetical precursor of columbin (e.g. IV) must be a diterpene of the "wrong", or reversed, configuration. Indeed, the terpenoid lactones, iresin[7] and andrographolide,[8] which have this type of configuration may be closely related to this precursor.

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[7] C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, J. Amer. Chem. Soc. 76, 6410 (1954).

[8] M. P. Cava and Boris Weinstein, Chem. & Ind. 851 (1959).

Tetrahedron Letters No. 15, pp. 5-9, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

JATAMANSONE

T. R. Govindachari, B. R. Pai, K. K. Purushothaman and S. Rajadurai

Department of Chemistry, Presidency College, Madras, India

(Received 4 August 1959)

THE results of our degradation studies on jatamansone,[1] the sesquiterpene ketone from Nardostachys jatamansi are reported here. Jatamansone was recovered unchanged after refluxing with 60 per cent sulphuric acid for 12 hr or after treatment with saturated ethereal hydrogen chloride for 48 hr. Wolff - Kishner reduction of jatamansone yielded the saturated hydrocarbon jatamansane, $C_{15}H_{28}$, b.p. 90°/0.5 mm. Analytical results on jatamansone, its derivatives and all the degradation products mentioned in the sequel were consistent with the formulation of jatamansone as $C_{15}H_{26}O$, which should therefore be a saturated bicyclic ketone.

Dehydration of jatamansol with PBr_3 - aniline yielded jatamansene, $C_{15}H_{26}$, b.p. 106-108°/4 mm, which on ozonolysis gave a dialdehyde, $C_{15}H_{26}O_2$, b.p. 138°/1 mm. The dialdehyde was converted by refluxing with alcoholic

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[1] T. R. Govindachari, S. Rajadurai and B. R. Pai, Chem. Ber. 91, 908 (1958).

hydrochloric acid to an α:β-unsaturated aldehyde, $C_{15}H_{24}O$, b.p. 144°/1.2 mm, yielding a red 2:4-dinitrophenylhydrazone, m.p. 168° (from methanol), obtained also directly from the dialdehyde. The dialdehyde was oxidised by hydrogen peroxide to a diacid, jatamansic acid, $C_{15}H_{26}O_4$, obtained earlier[1] by the chromic acid oxidation of jatamansone. With excess benzaldehyde, either under acid or base catalysis, jatamansone formed only a monobenzylidene derivative, which yielded jatamansic acid on ozonolysis. It can be concluded that the formation of jatamansic acid does not involve any prior rearrangement of the carbon skeleton of jatamansone.

Jatamansone showed infra-red absorption at 1699 cm^{-1}, which could be ascribed to a 2,2-dialkylcyclohexanone system.[2] With one mole of bromine, a monobromojatamansone, $C_{15}H_{25}OBr$, m.p. 105°, was formed (infra-red absorption at 1729 cm^{-1}, equatorial α-bromine). With excess bromine, only a dibromojatamansone, $C_{15}H_{24}OBr_2$, b.p. 145°/0.6 mm was formed (infra-red absorption at 1724 cm^{-1}). Since the presence of a $-CO-CH_2-$ group has been established, these results indicate that the other carbon adjacent to the carbonyl group is fully substituted.

Pyrolysis of jatamansic acid yielded norjatamansone, $C_{14}H_{24}O$, b.p. 110°/4 mm, showing carbonyl absorption at 1735 cm^{-1} (cyclopentanone). With excess benzaldehyde, norjatamansone yielded a monobenzylidene

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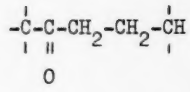
[2] E. J. Corey, T. H. Topie and W. A. Wozniak, J. Amer. Chem. Soc. 77, 5415 (1955).

derivative, b.p. 160°/0.2 mm (carbonyl band at 1709 cm^{-1}), yielding on ozonolysis a diketone, $C_{14}H_{22}O_2$, b.p. 140°/0.3 mm, oxidized by sodium metaperiodate to norjatamansic acid, $C_{14}H_{24}O_4$, m.p. 143°, forming an anhydride, m.p. 85-86°, having carbonyl bands at 1757 and 1805 cm^{-1} (glutaric anhydride). Norjatamansic anhydride yielded, with excess bromine, a monobromo derivative, $C_{14}H_{21}O_3Br$, m.p. 143°, converted by treatment with dimethylaniline to dehydronorjatamansic anhydride, $C_{14}H_{20}O_3$, m.p. 153° (λ_{max} 225 mμ, log ε, 3.67, infra-red bands at 1786, 1672 and 1595 cm^{-1}). Dehydronorjatamansic anhydride was recovered unreacted after treatment with ozone and no volatile product like formaldehyde or acetone could be detected in the reaction mixture. A terminal methylene group or an isopropylidene group was not likely to be present in this compound. Dehydronorjatamansic anhydride dissolved in alkali but acidification of the alkaline solution yielded the anhydride directly, the intermediate acid not being isolable.

Oxidation of jatamansic acid (or jatamansone) with manganese dioxide - sulphuric acid (60 per cent) yielded trimellitic acid, whose formation should not have involved any rearrangement prior to dehydrogenation, since jatamansic acid was recovered unchanged together with some norjatamansone under the same conditions, in the absence of manganese dioxide. Dehydrogenation of norjatamansic acid with Pd-C yielded a benzenoid hydrocarbon (λ_{max} 265 mμ), oxidized by manganese dioxide - sulphuric acid to trimellitic acid.

The degradation results outlined establish that:

(1) jatamansone has a carbonyl-containing ring, which is six-membered, and that this ring includes the structural feature



(2) the second ring is also six-membered

(3) 1:3-fusion of the two six-membered rings is unlikely, since in that case, the formation of dehydrojatamansic acid would involve violation of Bredt's rule. The two six-membered rings should be 1:2-fused.

It had been reported earlier[1] that dehydrogenation of jatamansol yielded a bluish-violet azulene. This has now been purified by chromatography on paraffin-impregnated paper[3] and freed from blue, reddish-violet and violet azulenes present in trace amounts and has now been found to yield a trinitrobenzene adduct, m.p. 158°, not identical with the trinitrobenzene adducts of any of the natural azulenes. It has not been possible to obtain a naphthalenic product from the dehydrogenation of jatamansol, jatamansone or jatamansene under a variety of conditions. A plausible explanation[4] for the formation of an azulene from a naphthalene precursor could be suggested, but it is hoped that further work in progress will resolve the conflicting results obtained in degradation and dehydrogenation reactions and settle the structure of jatamansone.

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[3] O. Knessl and A. Veastiborova, Coll. Czech. Chem. Comm. 19, 782 (1954); M. Romanuk, V. Herout and F. Sorm, Ibid. 21, 894 (1956).

[4] Cf. D. H. R. Barton and P. de Mayo, J. Chem. Soc. 150 (1957).

Acknowledgement - We are grateful to the Government of India for the award of a National Research Fellowship (to S.R.), the Government of Madras for a Research Assistantship (to K.K.P.), Dr. N. Sheppard for some infra-red spectra and the India Wheat Loan Administration for gift of an Infra-cord Spectrophotometer.

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ÜBER DEN MECHANISMUS DER WASSERSTOFFÜBERTRAGUNG MIT PYRIDINNUCLEOTIDEN - XVIII.[1]

NICHTENZYMATISCHE REDUKTION VON BRENZTRAUBENSÄURE MIT EINEM DPNH-MODELL

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(Received 5 August 1959)

VOR kurzem zeigten Abeles und Westheimer,[2] dass α-Ketosauren durch Erhitzen mit 2,6-Dimethyl-3,5-dicarbäthoxy-1,4-dihydropyridin, das man durch Hantzsch-Synthese erhält, zu α-Hydroxysäuren reduziert werden können. Die Reaktion verläuft unter direktem H-Transfer. Mit echten DPNH-Modellen, d.h. 1,4-Dihydropyridinen, die am Stickstoff alkyliert sind, konnte eine derartige Reaktion bisher nicht durchgeführt werden. Wie wir jetzt gefunden haben, lässt sich Brenztraubensäure unter analogen Bedingungen, wie sie Abeles und Westheimer benutzten, und mit etwa gleicher Ausbeute reduzieren, wenn das in der XIV. Mitteilung[3] dieser Reihe beschriebene

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[1] XVII. Mitteilung: K. Wallenfels und M. Gellrich, Chem. Ber. 92, 1406 (1959).

[2] R. Abeles und F. H. Westheimer, J. Amer. Chem. Soc. 80, 5459 (1958); D. Mauzerall und F. H. Westheimer, J. Amer. Chem. Soc. 77, 2261 (1955).

[3] K. Wallenfels, D. Hofmann und H. Schüly, Liebigs Ann. 621, 188 (1959).

N_1-(2,6-Dichlorbenzyl)-5-(2,4-dinitrophenylsulfenyl)-1,4-dihydronicotinsäureamid (I) als Wasserstoffdonator benutzt wird.

Wir erhitzten das Dihydropyridin 24 Std. lang mit Brenztraubensäure im geschlossenen Rohr auf 80° und bestimmten anschliessend die gebildete Milchsäure mit Hilfe der DPN^+-unabhängigen Milchsäuredehydrogenase nach Wieland.[4] Hierbei stört, wie wir uns überzeugt haben, auch ein grosser Uberschuss von Brenztraubensäure nicht. Die Ausbeute betrug, auf Dihydropyridin berechnet, 5-7%. Ausserdem wurde die Milchsäure papierchromatographisch aus dem Reaktionsgemisch abgetrennt und nachgewiesen. Ein Kontrollversuch unter gleichen Bedingungen ohne Dihydropyridin, liess keine Spur von Milchsäurebildung erkennen. Wir sind daher sicher, dass auch in unserem Falle ein H-Transfer vom Dihydropyridin zur Ketosäure stattgefunden hat.

Die Primarreaktion durfte in einer Addition von Brenztraubensäure an die C_5,C_6-Doppelbindung des Dihydropyridins bestehen. Ein derartiges Addukt, das ein Tetrahydropyridinderivat darstellt, lässt sich präparativ durch gelindes Erwärmen des roten Dihydropyridins (I) mit Brenztraubensäure gewinnen. Es kristallisiert in gelben Nadeln (Fp:140-143°C Zers.) und spaltet beim Erwärmen in Methanol 1 Mol Brenztraubensäure ab, die mit Milchsäuredehydrogenase und DPNH[5] bestimmt wurde. Das rote Dihydropyridin (I) wird quantitativ zurückerhalten.

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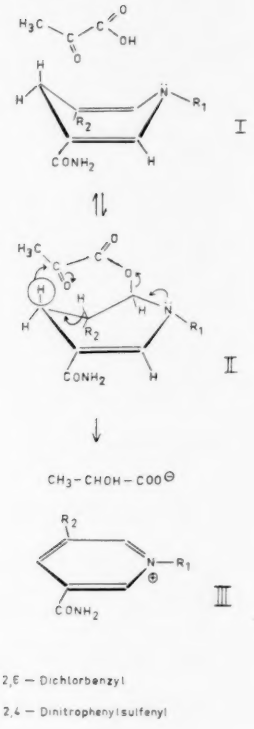
[4] O. Wieland, Biochem. Z. 329, 568 (1958).
[5] F. Kubowitz und P. Ott, Biochem. Z. 314, 94 (1943).



Wir formulieren daher die beschriebene Wasserstoffübertragung, die als Modellfall für die enzymatische Reduktion von α-Ketosäuren angesehen werden kann, als intramolekulare Hydridwanderung vom C_4-Atom des Tetrahydropyridinringes zur polarisierten Carbonylgruppe im Addukt (II).[6]

Durch Abspaltung des Lactatrestes bildet sich unmittelbar das durch Resonanz bevorzugte Pyridiniumlactat (III). Die Isolierung des kristallisierten Intermediärproduktes (II) stellt somit eine neue Stütze für die Annahme eines polaren Mechanismus der Wasserstoffübertragung mit Pyridinnucleotiden dar.[7]

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Wir danken Herrn Professor Dr. O. Wieland, München, für die Überlassung der Milchsäuredehydrogenase und Herrn F. Kubowitz für die Ausführung der enzymatischen Teste.

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[6] Wir formulieren das Addukt in der angegebenen Weise auf Grund von Studien am Stuart-Briegleb-Kalotten-Modell.

[7] Siehe dazu: K. Wallenfels in Steric Course of Microbiological Reactions S. 10-36. Churchill, London (1959).

Tetrahedron Letters No. 15, pp.14-18, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE CONVERSION OF D-ISOIRIDOMYRMECIN INTO D-IRIDOMYRMECIN

R. H. Jaeger and Sir Robert Robinson

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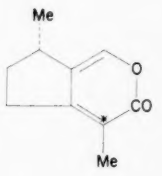
(Received 31 August 1959)

THE two iridolactones iridomyrmecin and isoiridomyrmecin are represented by the structure (I), the position α to the lactone carbonyl being epimerizable, but the configuration at this asymmetric centre (marked by an asterisk) has not yet been assigned. Previous work[1,2] indicates, however, that the configuration corresponding to isoiridomyrmecin appears to be the more stable of the two, since 83 per cent conversion into this epimer has been obtained by treatment of iridomyrmecin with alcoholic alkali.



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A polarimetric examination[2] of the epimerization of isoiridomyrmecin with sodium ethoxide in absolute ethanol revealed a complex reaction and led to the conclusion that the equilibration gave a 14 per cent conversion into iridomyrmecin, which complements the 83 per cent conversion of iridomyrmecin $[\alpha]_D^{20}$ + 210° into isoiridomyrmecin $[\alpha]_D^{24}$ - 59°. From this equilibrated mixture only isoiridomyrmecin was isolated. Thus the epimerization of isoiridomyrmecin into iridomyrmecin and isolation of the latter from the reaction mixture had still to be accomplished and the present report described a method by which this was achieved.

The synthesis of D- and L-isoiridomyrmecin from D- and L-citronellal respectively has been described.[3] The latter was shown to be identical with the natural product isolated from the ant Iridomyrmex nitidus. D-Isoiridomyrmecin, however, is much more readily available, since D-citronellal is a commercial product and accordingly was used in preference to the L-isomer.

D-Isoiridomyrmecin $[\alpha]_D^{28}$ + 60° was refluxed for 48 hr with quinoline. The liquid reaction product had $[\alpha]_D^{27}$ - 41° which represents a 37.5 per cent conversion into iridomyrmecin. The equilibrated mixture was separated at a low temperature by crystallization from light petroleum into two portions of approximately equal weight: (i) a material which was crystalline at

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[1] R. Fusco, R. Trave and A. Vercellone, Chim. e Industr. 37, 251 (1955).

[2] G. W. K. Cavill and H. D. Locksley, Aust. J. Chem. 10, 352 (1957).

[3] K. J. Clark, G. I. Fray, R. H. Jaeger and Sir Robert Robinson, Angew. Chem. 70, 704 (1958); Tetrahedron 6, 217 (1959).

-15° but was liquid at toom temperature $[\alpha]_D^{27}$ -23°; (ii) a liquid recovered from the mother liquor, $[\alpha]_D^{27}$ -65°. This specific rotation corresponds to 46 per cent iridomyrmecin being present in this fraction. A solution of the material in light petroleum was chromatographed on neutral alumina; arbitrary fractions were collected and the rotation of each eluate was determined. It was found that although no clear-cut separation of the two epimers could be effected in this way, light petroleum eluated material containing a high proportion of iridomyrmecin. By repeating the chromatography with the fractions having the highest negative rotation, pure D-iridomyrmecin, m.p. 61-62°, $[\alpha]_D^{29}$ -207° was eventually obtained. The infra-red spectrum of this material was

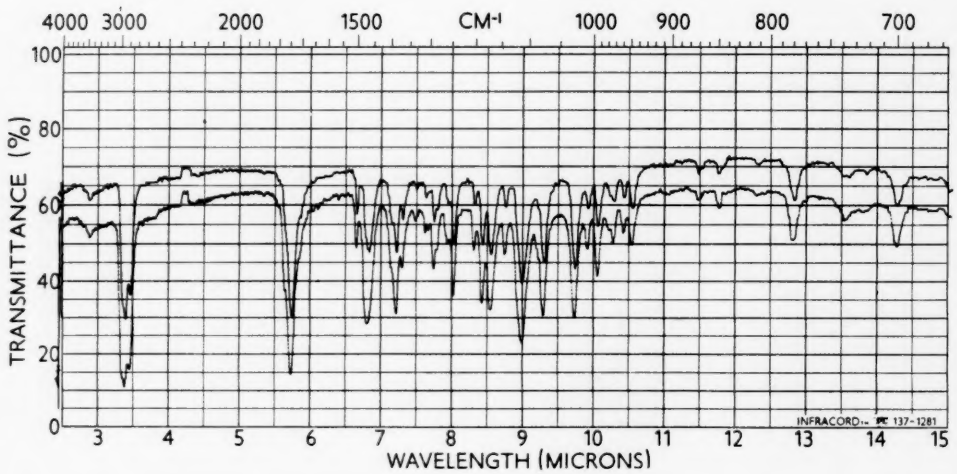

FIG. 1. Top: D-Iridomyrmecin (synthetic)

Bottom: L-Iridomyrmecin (natural).

indistinguishable from that of its enantiomorph, the natural product L-iridomyrmecin, m.p. 61-62°, $[\alpha]_D^{20}$ + 210° [1] (cf. Fig. 1).

With the completion of this work it has now been demonstrated that the three terpenoid compounds isolated from various Iridomyrmex ants, i.e. iridomyrmecin, isoiridomyrmecin and iridodial, can be synthesized from citronellal.

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A racemic mixture prepared by crystallizing equal weights of D- and L-iridomyrmecin from light petroleum had m.p. 59.5° and no measurable rotation.

Experimental

Infra-red spectra of D- and L-iridomyrmecin were determined in Nujol mulls. Light petroleum without specification means the fraction of b.p. 40-60°. Ethereal extracts were dried over anhydrous magnesium sulphate. Rotations were determined at c, 1.0 in CCl_4.

Epimerization of D-isoiridomyrmecin. D-Isoiridomyrmecin $[\alpha]_D^{28}$ + 60° (1.42 g) was refluxed with quinoline (70 cc) for 48 hr in an atmosphere of nitrogen. The reaction mixture was poured into hydrochloric acid internally cooled with crushed ice. The product was collected in ether, the ethereal layer washed successively with water, aqueous sodium hydrogen carbonate and water. The dried extract was freed from solvent and the residue evaporatively distilled at 80-90°/0.4 mm (bath temperature). The colourless oil (1.39 g), $[\alpha]_D^{27}$ -41° solidified at -15°; a little light petroleum was added and the material allowed to dissolve almost completely at room temperature. When only a few crystals remained undissolved the mixture was again chilled at -15° which caused crystallization of part of

the product. The supernatant solution was removed with a pipette, and the solvent evaporated. The crystalline material (695 mg) melted at room temperature and had $[\alpha]_D^{27}$ -23°. The residue recovered from the mother liquor was a liquid (696 mg), $[\alpha]_D^{27}$ -65°.

A solution of the latter material in a little light petroleum was adsorbed on neutral alumina (75 g); the same solvent eluted some impure material (15 mg), followed by crystalline material (77 mg), $[\alpha]_D^{28}$ -192°; light petroleum (b.p. 60-80°) eluted more crystalline material (68 mg), $[\alpha]_D^{28}$ -152°; a 4:1 mixture of light petroleum (b.p. 60-80°) - benzene eluted a yellow oil (206 mg), $[\alpha]_D^{28}$ -96°; the material eluted with benzene was a crystalline solid (55 mg), $[\alpha]_D^{28}$ + 12°. The crystalline portions possessing the highest negative rotations were united and re-chromatographed to yield D-iridomyrmecin (76 mg) which crystallized from light petroleum (b.p. 30-40°) as beautiful elongated colourless prisms, m.p. 61-62°, $[\alpha]_D^{29}$ -207° (Found: C, 71.7; H, 9.7. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.5%). The infra-red spectrum of this compound was absolutely indentical with that of natural L-iridomyrmecin (kindly provided by Professor M. Pavan), m.p. 61.5 - 62.5° $[\alpha]_D^{20}$ + 210° (cf. Fig. 1).

D,L-Iridomyrmecin. A sample prepared by crystallizing a mixture of equal weights of D- and L-iridomyrmecin from light petroleum had m.p. 59.5° and no measurable rotation. This accords with the results of Korte et al.[4] who ascribe the m.p. 59° to synthetic DL-iridomyrmecin.

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[4] F. Korte, J. Falbe and A. Zschocke, Tetrahedron 6, 201 (1959).

Tetrahedron Letters No. 15, pp. 19-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

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SOME OBSERVATIONS CONCERNING THE COPPER SALT CATALYZED REACTIONS OF t-BUTYL PERBENZOATE WITH OLEFINS[1]

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(Received 26 August 1959)

IT has been reported[2-5] that catalytic amounts of certain transition metal salts can markedly modify the course of many reactions of organic peroxides with a wide variety of organic substances. One of the most interesting reactions found was that between olefins and t-butyl peresters in the presence of copper or cobalt salts.[2,6] The reaction has been reported to be specific, i.e. only one product, the 3-substituted olefin, is formed from

$$R\text{-}CH{=}CH_2 + C_6H_5CO_3C(CH_3)_3 \xrightarrow[\text{Salt}]{\text{Cu}} R\text{-}\underset{\displaystyle O_2CC_6H_5}{\underset{|}{CH}}\text{-}CH{=}CH_2 + (CH_3)_3COH$$

terminal olefins.[2,6] These findings have now been corroborated, since

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[1] Supported by the Alfred P. Sloan Foundation and the Colgate-Palmolive Company.

[2] M. S. Kharasch and G. Sosnovsky, J. Amer. Chem. Soc. 80, 756 (1958).

[3] M. S. Kharasch and G. Sosnovsky, Abstracts of Papers presented at the 134th Meeting of the American Chemical Soc., Chicago, September 1958, p. 7P.

[4] M. S. Kharasch and A. Fono, J. Org. Chem. 23,324 (1958).

[5] M. S. Kharasch and A. Fono, J. Org. Chem. 24, 606 (1958).

[6] M. S. Kharasch, G. Sosnovsky and N. C. Yang, J. Amer. Chem. Soc. In press.

allylbenzene gave no cinnamyl benzoate. Of equal importance is the finding that propenylbenzene gave only cinnamyl benzoate. Thus, the two isomeric olefins yielded unrearranged products. These experiments show that these materials do not form a common intermediate, such as an allyl radical, carbonium ion or carbanion during the reaction. The evidence that these reactions are modified radical reactions is mainly circumstantial.[5] However, it is all reasonable.

The reaction of cyclohexene and t-butyl perbenzoate-carbonyl-O^{18} in the presence of cupric ion afforded cyclohexenyl benzoate, which was reduced (H_2/Pd) to cyclohexyl benzoate, which in turn was reduced (LAH) to cyclohexanol and benzyl alcohol. The oxygen-18 analytical data showed that the label was completely equilibrated between the two oxygens of the cyclohexenyl benzoate. The equilibration must have occurred during the formation of the unsaturated ester, since equilibration after its formation would necessarily lead to a mixture of allylic isomers. Any mechanism which does not permit equilibration is excluded. Such mechanisms are in general those which involve a concerted reaction of perester, olefin and catalyst.

The reaction of 3-deuterio-3-phenylpropene with t-butyl perbenzoate in the presence of cupric ion at 90° followed by deuterium analysis of the product showed that the isotope effect (k_H/k_D) for the hydrogen abstraction from the labeled allylbenzene was 4.3. The isotope effect is larger than one would predict for a simple hydrogen abstraction from allylbenzene by a t-butoxy radical. For example, Wiberg and Slaugh[7] have studied the deuterium isotope effects for the abstraction of hydrogen from toluene at 80° by several radicals. Their results are as follows: succinimide radical,

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4.86; bromine atom, 4.59; and for the system ethylbenzene-succinimide radical, 2.67. One would predict that radical abstraction of hydrogen from allylbenzene would be more facile than from toluene or ethylbenzene. Therefore, for any given abstracting radical, allylbenzene would show the smallest isotope effect. The data in the literature concerning the reactivity of alkoxy radicals does not permit a quantitative comparison to that of a succinimide radical or bromine atom. All of the data[8,9] does indicate that a t-butoxy radical is more reactive than a succinimide radical. This being the case, the predicted isotope effect for the reaction of allylbenzene with a t-butoxy radical would be less than 2.67 and probably less than 2.0. One can conclude, therefore, with a high degree of certainty, that the hydrogen abstraction is not a simple reaction of a t-butoxy radical with allylbenzene. One also concludes this from the nature of the products obtained from isomeric olefins, since simple abstractions would give an allyl radical and ultimately lead to the same products from the isomeric olefins.

Although these data and the other available data[2,6] do not permit the postulation of a definitive mechanism, a satisfactory working hypothesis can be suggested. It is proposed that the copper ion reacts with t-butyl perbenzoate to give a complex of the copper ion with a t-butoxy radical and a benzoyloxy radical. This complex can co-ordinate with the olefin

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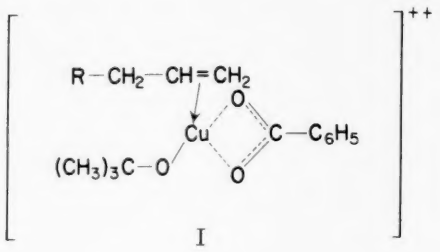
[7] K. B. Wiberg and L. H. Slaugh, J. Amer. Chem. Soc. 80, 3033 (1958).

[8] C. Walling, B. Jacknow and W. Thaler, Abstracts of Papers presented at the 136th Meeting of the American Chemical Soc. Atlantic City, September, 1959, p. 54P.

[9] C. Walling, Free Radicals in Solution. John Wiley, New York (1957).

to give an intermediate (I), for which many resonance structures are available.



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Collapse of I can occur by hydrogen abstraction by the complexed t-butoxy radical which gives t-butyl alcohol and the appropriate complexed olefinic radical. Rapid combination within the copper complex of the olefinic radical and the benzoyloxy group leads to the product. This scheme accounts for the large isotope effect since the complexed t-butoxy radical will be less reactive than a free t-butoxy radical. One predicts that the complexed olefin will be less reactive towards hydrogen abstraction than the uncomplexed olefin. However, the overall rate may be greater because of a favourable entropy effect. Such a complex also accounts for the equilibration of the label in the benzoyloxy group and explains the fact that carbon dioxide is not formed when t-butyl peracetate is used, since a free acetoxyl radical loses carbon dioxide spontaneously.[10]

Further work is now in progress on these reactions. Of particular

interest will be the outcome of a stereochemical study now in progress.[11]

Acknowledgement - The authors are grateful to Prof. N. C. Yang for many helpful discussions and exchanges of experimental results.

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[10] Reference 9, p. 493.

[11] Prof. N. C. Yang, University of Chicago, private communication.

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Tetrahedron Letters No. 16, pp.1-8, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE CONSTITUTION OF ECHINULIN

C. Cardani, G. Casnati, F. Piozzi and A. Quilico

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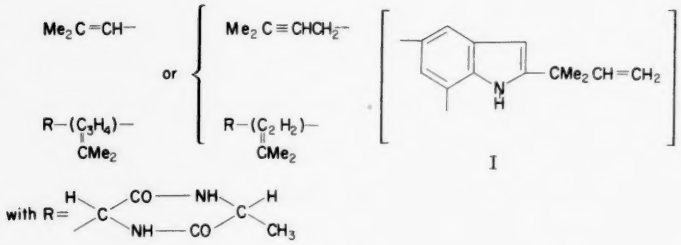
(Received 14 September 1959)

PREVIOUS investigations on <u>echinulin</u>,[1] $C_{28}H_{37}O_2N_3$, an important constituent of the mycelium of the moulds of the <u>Aspergillus glaucus</u> group, had led us to assign to this substance partial formula (I).



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[1] Previous communications: A.Quilico, F. Piozzi and C. Cardani,

The attribution of a $-CH_2-$ group to the alkenic side chain or to the bridge which links the indole and diketopiperazine moieties of the molecule was still uncertain, and the absolute location of the two substituents in 5- and 7-positions of the indole ring remained undetermined.

We succeeded in solving the first of these problems by a thorough re-examination of the oxidative degradation products (fatty acids and non-volatile aliphatic acids) of hydroechinulin, $C_{28}H_{43}O_2N_3$, echinulin itself, and of the 2,5,7-trisubstituted indoles which are formed by alkaline pyrolysis of echinulin and its hydroderivative.[2] The identification of the fatty acids obtained on oxidation in different conditions was achieved by vapour phase chromatography, whereas the non-volatile acids were characterized by paper chromatography and then isolated in amounts sufficient for the chemical identification by chromatography on column of silicagel. Drastic oxidation of hydroechinulin with nitric acid, alkaline permanganate, acidic permanganate, with continual steam distillation of the fatty acids formed, gave the following acids: acetic, isobutyric, isovaleric, α,α-dimethylbutyric and isocaproic. Of these, the first four acids had been already isolated in earlier degradative work,[3] whereas isocaproic acid had not yet been identified. Its quantity depends on the nature of the oxidant and on the more or less drastic conditions in which the oxidation has been carried out. The obtaining of isocaproic acid indicates

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Gazz. Chim. Ital. 88, 125 (1958), C. Cardani, G. Casnati, B. Cavalleri and A. Quilico, Rend. Accad. Lincei [8] 24, 488 (1958).

2 A. Quilico, C. Cardani and F. Piozzi, Gazz. Chim. Ital. 85, 3 (1955).

3 A. Quilico and C. Cardani, Gazz. Chim. Ital. 83, 155 (1953).

that hydroechinulin contains the C_5 side chain (II) or (III), which must be present in its unsaturated form (IV) or (V) in echinulin itself.

$Me_2CHCH_2CH_2$-(C) II

$Me_2CHCH_2CH\begin{matrix}(C)\\(C)\end{matrix}$ III

$Me_2C{=}CHCH_2$-(C) IV

$Me_2C{=}CHCH\begin{matrix}(C)\\(C)\end{matrix}$ V

This fact is also confirmed by the isolation, among the non-volatile nitric acid oxidation products of hydroechinulin, of the α-hydroxy-α-methyl-glutaric acid lactone, m.p. 69°, easily reduced by HI and P to α-methyl-glutaric acid, m.p. 78°. Considerable amounts of the lactonic acid are also formed on nitric acid oxidation of the indole from alkaline pyrolysis of hydroechinulin, and it can be reasonably assumed that both isocaproic acid and the lactonic acid take their origin from the same side chain (II) or (III).[4]

The demonstration that echinulin actually contains an isopentenyl group (IV) directly attached to the benzene ring has been achieved by the study of the products of its alkaline cleavage. On prolonged treatment at 200° with ethanolic KOH, migration of the double bond of (IV) to the

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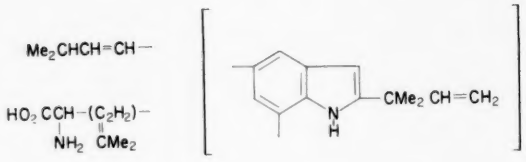
[4] It is known that isocaproic acid yields the α-hydroxy-α-methyl-glutaric acid lactone by drastic nitric acid oxidation. Cf. J. Bredt, Ber. 14, 1780 (1881).

conjugated position with the benzene system occurs conjointly with the hydrolysis of the diketopiperazine ring, giving alanin and the indole aminoacid isoechinin $C_{25}H_{34}O_2N_2$ (VI).



VI

Catalytic hydrogenation of (VI) affords the corresponding saturated hydroechinin, $C_{25}H_{40}O_2N_2$, which can also be obtained by hydrolysis of hydroechinulin with ethanolic KOH at 200°. Ozonolysis in acetic acid of iso-echinin yields a mixture of volatile carbonyl compounds; chromatographic analysis on silica gel column of the corresponding 2:4-dinitrophenyl-hydrazones gave the dinitrophenylhydrazones of formol, acetone and isobutanal in the almost theoretical molecular ratios (1:1:1) required by formula (VI). Echinulin with the same treatment yielded formol and acetone dinitrophenylhydrazones in about 1:2 molecular ratios.

Conclusive evidences for the presence of side chain (IV) and not (V) have been supplied by the study of the U.V. and I.R. spectra of echinulin

and its transformation products. The U.V. spectra of echinulin and its hydroderivative are practically identical, and the same can be said for those of the deoxybases (deoxyechinulin and deoxyhydroechinulin) which are formed on reduction with lithium aluminium hydride.[5] This indicated that none of the three double bonds of the non-hydrogenated products are conjugated with the indole system. On the contrary, strong differences are noticeable in the U.V. spectra of iso-echinin (VI) (in EtOH λ_{max} 255 mμ, log ε 4.65; λ_{max} 310 mμ, log 3.66) and its hydrogenated derivative hydroechinin (in EtOH λ_{max} 228 mμ, log ε 4.58; λ_{max} 286 mμ, log ε 3.93). The bathochromic shift of the maxima in iso-echinin can be attributed to conjugation of the double bond of the isopentenylic chain with the benzene ring. In hydroechinin the maxima are in the same positions as in echinulin and hydroechinulin. Moreover, the I.R. spectrum of iso-echinin shows a neat band at 965 cm^{-1} which can be assigned to a <u>trans</u> -CH=CH- group. This band, which is not present in the echinulin I.R. spectrum, demonstrates that the drastic alkaline treatment has caused the shift:

$$Me_2C{=}CHCH_2\text{-benzene ring} \longrightarrow Me_2CHCH{=}CH\text{-benzene ring.}$$

On the basis of similar chemical and spectrochemical evidence we concluded that the unsaturated 2,5,7-trisubstituted indole which is formed in the alkaline pyrolysis of echinulin is actually a mixture of at least two substances of which one contains chain (IV) as in echinulin, and the other is the <u>isobase</u> in which the double bond of (IV) has shifted into conjugation with the

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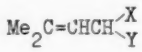
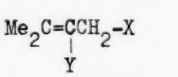
[5] A. Quilico, F. Piozzi and C. Cardani, <u>Gazz. Chim. Ital.</u> <u>88</u>, 125 (1958).

benzene ring. Indoles with a different degree of unsaturation and possibly with different a number of carbon atoms are probably present in the mixture.

Further information on the structure of the C_5 bridge which unites the indole and diketopiperazine moieties of echinulin is supplied by the fact that both echinulin and its hydroderivative are racemized by sodium ethoxide in ethanol solution at ordinary temperature. This would indicate that echinulin does not contain extra asymmetry centres except the two belonging to the diketopiperazine ring. This permits us to discard structure (VII) which would also give acetone on ozonolysis and leaves structure (VIII) as the only one possible for the bridge.



VII



VIII

The alkaline pyrolysis of echinulin and hydroechinulin still needs a closer investigation,* but its results are best accounted for when in (VIII) Y is the diketopiperazine moiety. Taking into account the previous degradative work and other considerations that will be discussed in a more detailed paper, we can safely conclude that echinulin possesses either constitution (IX) or (X), in which the substituents in the 5- and 7-positions of the indole ring have been exchanged.

Other considerations, in particular the obtaining of cryptoechinulinic acid on permanganate oxidation of hydroechinulin,[6] would suggest formula (IX)

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* Experiments on models are in progress.

[6] A. Quilico and C. Cardani, Gazz. Chim. Ital. 83, 155 (1953).

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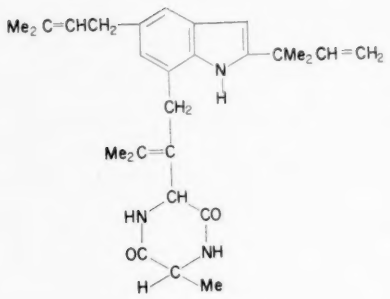
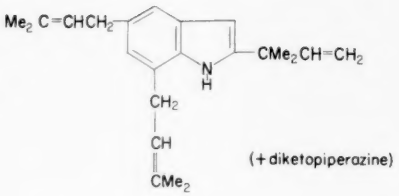


IX (X)

as the most probable. The isopentanic nature of the two side chains and of the bridge is evident in both. Echinulin would therefore take its origin from the condensation of an indole containing three isoprene units in 2-, 5- and 7-positions with a molecule of glycine and one of L(+)alanine.

Note. On the occasion of the meeting of the Tetrahedron Honorary Editorial Advisory Board held in Munich on 4 September 1959, Professor A. J. Birch kindly informed me that biosynthetic work still in progress by himself H. Smith and R. A. Blance with 2-^{14}C-mevalonic acid and Me$^{14}CO_2H$ clearly indicates that the most probable skeleton for echinulin is (XI).



XI

This brilliant result is in perfect agreement with the conclusions we have reached on the basis of purely chemical and spectrochemical evidences, and further supports the suggested alternative formulae (IX) and (X). — A.Q.

Tetrahedron Letters No.16, pp.9-16, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE METHYLATION OF PYRONONES. THE STRUCTURAL CORRELATION OF AUREOTHIN AND ISOAUREOTHIN

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(Received 16 September 1959)

WE have investigated [1-6] the structure of aureothin (I), a yellow toxin isolated [7] from the culture of Streptomyces thioluteus. The substance is exceedingly sensitive towards acidic reagents and is easily demethylated with dilute acids to give desmethylisoaureothin (II). Spectral data indicate the presence of an α-pyrone rather than a γ-pyrone structure in (II), as is formulated below. Methylation of (II) with diazomethane under the usual condition yielded an isomer of aureothin, isoaureothin (III),

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[1] Y. Hirata, K. Okuhara and T. Naito, Nature 173, 1101 (1954).

[2] Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, J. Chem. Soc. Japan 78, 1700 (1957).

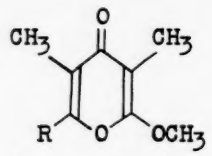
[3] T. Naito, Y. Hirata, K. Okuhara and K. Iwadare, J. Chem. Soc. Japan 79, 374 (1958).

[4] H. Nakata, Y. Hirata, K. Okuhara, K. Yamada, T. Naito and K. Iwadare, J. Chem. Soc. Japan 79, 379 (1958).

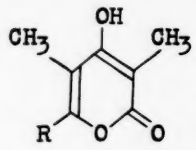
[5] K. Yamada, Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, J. Chem. Soc. Japan 79, 384 (1958).

[6] Y. Hirata, H. Nakata and K. Yamada, J. Chem. Soc. Japan 79, 390 (1958).

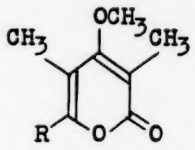
[7] K. Maeda, J. Antibiotics A 6, 137 (1953).



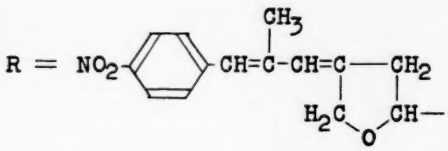
(I) aureothin



(II) desmethyl-isoaureothin



(III) isoaureothin



almost exclusively.

Recently, however, we have found that a little amount of (I) was also obtained from the reaction mixture only when a dilute ethereal solution of diazomethane was added gradually to a suspension of (II) in dry ether under the strictly anhydrous condition. The product ratio of the two isomeric ethers, (I)/(III) was 1/60.

Although literatures contain several references to the methylation reaction of 2,4-pyronone derivatives, the results obtained are still the subject of considerable controversy; thus, Arndt and Eistert [8] assigned the 6-methyl-4-methoxy-α-pyrone (A) structure for the methylation product of triacetic lactone (IV), while Arndt and Avan [9] later reported that treatment of (IV) with diazomethane yielded only one product, 6-methyl-2-methoxy-γ-pyrone (G). In 1952 Chmielewska and Cieslak [10] obtained the 1:3 mixture of two isomeric ethers, (G) and (A). Shortly thereafter, Janiszewska-Drabarek [11] re-examined this diazomethane methylation in

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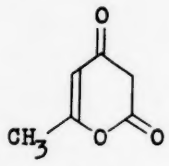
[8] F. Arndt and B. Eistert, Ber. 68, 1572 (1935).

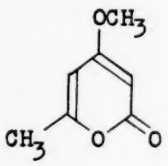
[9] F. Arndt and S. Avan, Ber. 84, 343 (1951).

[10] I. Chmielewska and J. Cieslak, Przemyst Chem. 8, 196 (1952).

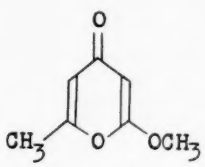
[11] S. Janiszewska-Drabarek, Roczniki Chem. 27, 456 (1953).



(IV)
triacetic lactone



(A)
6-methyl-4-methoxy-α-pyrone



(G)
6-methyl-2-methoxy-γ-pyrone

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detail and concluded that both (A) (72 % yield) and (G) (20 % yield) were produced in this reaction. On the other hand, Wiley and Jarboe [12] reported that only one isomer (A) was formed. Several results in other 2,4-pyronone derivatives were also reported. [13-18]

Recently, there appeared an extensive study [19] on the methylation of triacetic lactone (IV) and it was concluded that methylation of 2,4-pyronones such as (IV) with diazomethane usually yielded mixtures of the two possible isomers, the actual proportions depending on the nature of other substituents. [20] In the case of methylation of desmethylisoaureo-

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[12] R. H. Wiley and C. H. Jarboe, J. Am. Chem. Soc. 78, 624 (1956).
[13] W. Borsche and C. K. Bodenstein, Ber. 62, 2515 (1929).
[14] I. Chmielewska and J. Cieslak, Roczniki Chem. 28, 38 (1954).
[15] J. Cieslak, Roczniki Chem. 32, 837 (1958).
[16] I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik and K. Pitakowska, Tetrahedron 4, 36 (1958).
[17] R. B. Woodward and G. Small, Jr., J. Am. Chem. Soc. 72, 1297 (1950).
[18] E. Ziegler and E. Nolken, Monatsh. 89, 391 (1958).
[19] E. Herbst, W. B. Mors, O. R. Gottlieb and C. Djerassi, J. Am. Chem. Soc. 81, 2427 (1959).
[20] Chmielewska and co-workers observed that two series of isomeric methyl ethers were obtained on the methylation of 3-substituted 4-hydroxy-coumarins with diazomethane and the product proportions were distinctly affected by the type of substituent in position 3. We are indebted to Professor I. Chmielewska of Warsaw University for his kind information of this result (private communication to K. Y.). See, J. Cieslak, S. Lewak and I. Chmielewska, Roczniki Chem. 33, 349 (1959).

thin (II), however, the product ratio of the two isomeric ethers seemed to depend also on the reaction condition employed. [21]

Since it appeared of interest to investigate further the scope and mechanism of this reaction, the methylation reaction of triacetic lactone with diazomethane was re-examined in order to elucidate the relation between the reaction condition and the product proportions. Consequently, a dilute ethereal solution of diazomethane prepared [22] from 10 g of nitrosomethylurea was added, with vigorous stirring, to a suspension of 1 g of triacetic lactone (IV) in dry ether over various periods. All traces of atmospheric moisture were excluded and the temperature of the reaction mixture was maintained at 10 - 15° during the addition of the diazomethane solution. The resulting mixture was separated using the technique of Polish workers. [10,23] Product proportions are calculated as the percentage of the total weight of methylated products isolated. The results are summarized in Table 1.

On the basis of these data, it may be concluded that the product proportions of two isomeric ethers depend on the time required for the addition of the diazomethane solution; thus, the more gradually the addition of the diazomethane solution, the more will increase the proportions of the γ-pyrone methyl ether.

Triacetic lactone (IV) would exist in solution as a tautomeric mixture of (IVα) and (IVγ). Spectral data [10] suggest that in ether

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[21] Djerassi and co-workers [19] also noticed that different proportions were observed under the condition described by Wiley and Jarboe.[12]

[22] F. Arndt, in Organic Syntheses Coll. Vol. II, p. 165. John Wiley and Sons Inc., New York (1943).

[23] I. Chmielewska, J. Cieslak and T. Kraczkiewicz, Roczniki Chem. 30, 1009 (1956).

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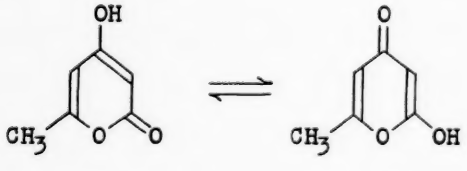
Table 1

	The time required for the addition of the diazomethane solution	Average product proportions	
i) Triacetic lactone (IV):		(G) %	(A) %
	very rapidly	0	100
	2 - 4 hours	26	74
	18 hours	33	67
ii) Desmethylisoaureothin (II):		(I) %	(III) %
	very rapidly	0	100
	2 - 4 hours	0	100
	18 hours	2	98

solution the tautomeric form of an α-pyrone structure (IVα) predominates. This means (IVγ) is thermodynamically less stable than (IVα). According to the general theory [24,25] proposed by Ingold in 1948, a proton is transferred more quickly to bases from the less stable tautomer than from the stable tautomer. This proton mobility is characterized as the "dynamic



(IVα) (IVγ)

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[24] A. G. Catchpole, E. D. Hughes and C. K. Ingold, J. Chem. Soc. 1948, 11.

[25] C. K. Ingold, Structure and Mechanism in Organic Chemistry p. 565. Cornell University Press, New York (1953).

acidity",[26,27] and therefore, (IVγ) has a larger dynamic acidity than that of (IVα). Since the reactivity towards diazomethane is proportional to this dynamic acidity, (IVγ) would react more rapidly than (IVα), though the equilibrium concentration of the former is much less than that of the latter in the solution.

When this solution reacts with a solution of diazomethane and only the direct methylation is possible, the following kinetic scheme can be written for the course of the reaction.

$$\begin{array}{ccccccc} CH_2N_2 & + & (IV\alpha) & \underset{k_-}{\overset{k_+}{\rightleftharpoons}} & (IV\gamma) & + & CH_2N_2 \\ & & \downarrow k_\alpha & & k_\gamma \downarrow & & \\ & & (A) & & (G) & & \end{array}$$

The velocity k_γ is larger than k_α so that the equilibrium quantity of (IVγ) will be used up more quickly than that of (IVα). Therefore, the prototropic rearrangement reaction (IVα)⟶(IVγ) will take place in favour of the formation of (G).

Arndt [26] has discussed in detail the "kinetic interplay" between methylation reactions (velocities k_α and k_γ) and prototropic rearrangement reactions (velocities k_+ and k_-), and drawn the following conclusions.
If the concentration of diazomethane is maintained at a low level by gradual addition of a dilute diazomethane solution to the reaction mixture, and all traces of water exerting catalytic influences are excluded, velocities k_α

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[26] F. G. Arndt, in J. Mitchell, Jr., I. M. Kolthoff, E. S. Proskauer and A. Weissberger ed., Organic Analysis Vol. I, p. 197. Interscience Publishers Inc., New York (1953).

[27] W. Hückel, Theoretische Grundlagen der Organischen Chemie Vol. I, 8th Ed., p. 306. Akademische Verlagsgesellschaft, Leipzig (1956).

and k_γ will decrease without a decrease in velocities k_+ and k_-; thus, there will be more time for the rearrangement (IVα)⟶(IVγ) to occur, and the condition will favour the formation of (G), i.e., its percentage will increase in the over-all product. This is in good agreement with our observations.

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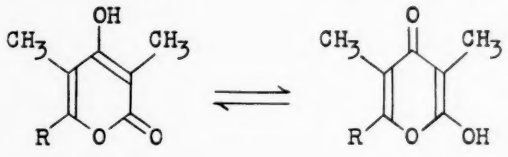
The same is true in the case of methylation of desmethylisoaureothin (II). As is shown in Table 1, aureothin (I) was obtained only when the diazomethane solution was added very gradually.

These data confirm the structural correlation of aureothin (I) and isoaureothin (III), and suggest that desmethyl derivative does exist in solution as a tautomeric mixture of (II) and (II'). Desmethylaureothin (II') has not been known so far, since its concentration in solution is very small as compared with that of the stable isomer, desmethylisoaureothin (II). It is interesting to note that aureothin (I) does not form a hydrochloride, though it has a γ-pyrone structure. Therefore, two isomers (I) and (III) were separated by fractional crystallization from alcohol.



(II) desmethyl-isoaureothin (II') desmethyl-aureothin

The more effective methylation reaction leading to a high yield of aureothin is neccessary for preparative purposes since the transformation would be involved in the final stage of the total synthesis of aureothin. Methylation with dimethyl sulfate gave satisfactory results; thus, the sodium salt of (II) prepared from 1 g of (II) was suspended in 40 ml dry

acetone and refluxed with 0.7 g of dimethyl sulfate for 6 hours. Upon employing the fractional crystallization of the resulting mixture, there was isolated 300 mg of aureothin (I) and 400 mg of isoaureothin (III).

As the methoxyl group can not be hydrolized under the reaction condition, the methylation reaction would be an irreversible process. The starting material is the least stable enolate anion and the kinetically controlled [24,25] methylation reaction would give the thermodynamically less stable isomer, aureothin (I). However, the methylation of the sodium salt of triacetic lactone (IV) under the same condition afforded only the stable isomer, 6-methyl-4-methoxy-α-pyrone (A).

The more detailed discussion of above results will be submitted for publication to the Journal of the Chemical Society of Japan in the near future.

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RUTILANTINONE

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University of Bristol

and J. J. Gordon

Antibiotics Research Station, Medical Research Council, Clevedon

(Received 24 September 1959)

DURING a survey of antiphage substances produced by actinomycetes, Dr. I. N. Asheshov of the Lister Institute, London, discovered the rutilantins which are produced by the actinomycete (strain A 220).[1] The rutilantins are a closely related group of deep red antibiotics; they are amphoteric and give salts including hydrochlorides, citrates, and picrates. Mild acid hydrolysis of rutilantin picrate has yielded the aglycone, rutilantinone, and carbohydrates some of which are basic. The determination of the structure of rutilantinone is now described.

Rutilantinone (deep red needles, m.p. 220°, with decomposition and dependence upon rate of heating; Found: C, 61.95; H, 4.70; OMe, 7.16; (C)-Me, 3.33. $C_{22}H_{20}O_9$ requires C, 61.68; H, 4.71; (1)OMe, 7.24; (1)(C)Me, 3.5) contains an acidic group, pKa' = 9.9 (90% ethanol)

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[1] I. N. Asheshov, Private communication.

(equivalent weight = 435 ± 20. $C_{22}H_{20}O_9$ requires 428). Alkaline hydrolysis of rutilantinone yielded a dibasic acid, pKa' 10.2 and 5.7 (90% ethanol) (equivalent weight = 215 ± 20) confirming the presence of an ester group [λ_{max} 1743 cm^{-1} (Nujol)]. This was shown to be a methyl ester since the alkyl iodide produced by hydriodic acid reacted with dimethyl aniline giving $Ph.NMe_3\}$ I which was identified by comparison (m.p. and I.R. spectrum) with an authentic specimen.

The environment of the (C)Me group in rutilantinone was determined by CrO_3 oxidation. This gave a mixture of steam volatile acids which yielded some p-bromophenacyl propionate identified by direct comparison (m.p. and I.R. spectrum). Thus rutilantinone contained a $\gtrless C\text{-}CH_2\text{-}CH_3$ group.

Rutilantinone tetracetate (m.p. 250°; Found: C, 60.51; H, 4.90; OMe, 5.83; OAc, 38.9. $C_{22}H_{16}O_5(OAc)_4$ requires C, 60.40; H, 4.74; OMe, 5.21; OAc, 39.3) showed complex absorption in the carbonyl region [λ_{max} 1781 cm^{-1} (phenolic acetate), 1743 cm^{-1} (ester), 1683 cm^{-1} (conjugated carbonyl) (in $CHCl_3$)] and it still contained at least one hydroxyl group [ν_{max} 3630 cm^{-1} (in $CHCl_3$)]. The ultra-violet and visible spectra of rutilantinone λ_{max} (ε_{max}) 234 mμ (43,100), 257 mμ (18,100), 293 mμ (7,250), 494 mμ (10,600), 525 mμ (8400) (in EtOH) [λ_{max} (ε_{max}) 234 mμ (50,300), 259 mμ (21,800), 290 mμ (8900), 486 mμ (13,000), 498 mμ (14,400), 520 mμ (12,000), 534 mμ (11,700) (in cyclohexane)] were quite characteristic of the 1,4,5-trihydroxyanthraquinone structure.[2,3]

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[2] J. H. Birkinshaw, Biochem. J. 59, 485 (1955).

[3] H. Brockmann and W. Muller, Chem. Ber. 92, 1164 (1959).

Its I.R. spectrum [λ_{max} 3520, 3400, 1611, and 1601 cm^{-1} (Nujol)] also showed that rutilantinone was a derivative of 1,4,5-trihydroxyanthraquinone.[4] These results led to the part structure (I) for rutilantinone in which the C_6H_{11} part contains a $-CH_2-CH_3$ unit.

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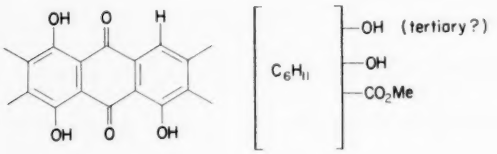

I

When rutilantinone was heated under reflux with toluene and a trace of toluenesulphonic acid, both hydroxyl groups were lost giving bisanhydrorutilantinone (m.p. 239°; yield ~ 80%; Found: C, 67.32; H, 4.09; OMe, 7.80; (C)Me 3.37. $C_{22}H_{16}O_7$ requires C, 67.34; H, 4.11; OMe, 7.92; (C)Me, 3.82). Bisanhydrorutilantinone showed no evidence of unbonded hydroxyl in its I.R. spectrum. Its ultra-violet and visible spectrum [λ_{max} (ε_{max}) 252 mμ (62,500), 275 mμ (36,700), 486 mμ (22,600), 496 mμ (24,200), 508 mμ (20,800), 519 mμ (25,500), 530 mμ (21,800) (in cyclohexane)] is identical in practically all respects with that of 1,4,6- and is different from 1,6,11-trihydroxytetracenequinone.[3]

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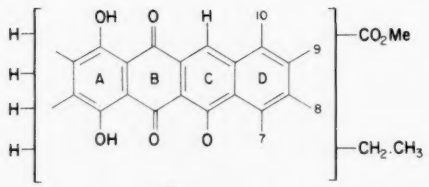
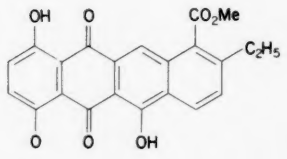
[4] H. Bloom, L. H. Briggs and B. Cleverley, J. Chem. Soc. 178 (1959).

Bisanhydrorutilantinone triacetate (m.p. 215°; Found: C, 64.58; H, 4.40; OMe, 6.07. $C_{28}H_{22}O_{11}$ requires C, 64.86; H, 4.28; OMe, 5.98) has a U.V. spectrum [λ_{max} (ε_{max}) 248 mμ (49,500), 299 mμ (28,500), 391 mμ (6800), 396 mμ (6860) (in MeOH)] almost identical with that of 1,4,6-triacetoxytetracenequinone. These facts lead to the part structure (II) for bisanhydrorutilantinone.

The ester group in bisanhydrorutilantinone (ν_{max} 1724 cm^{-1}) (cf. rutilantinone, ν_{max} 1743 cm^{-1}) cannot be located on ring A because it would then be ortho to a hydroxyl group. For this and other reasons it must be located on ring D. The ester group is so stable to hydrolysis by 2 N alkali that it must be flanked by two ortho substituents; it must be in positions 7 or 10 with the ethyl group correspondingly placed on 8 or 9. In all our experiments there has been no evidence for lactone formation so that position 10 for the $-CO_2Me$ group is preferred. This leads to structure (III) for bisanhydrorutilantinone which is also preferred on other grounds (vide infra).



II



III

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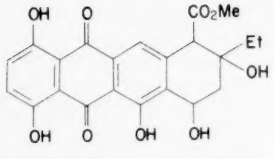
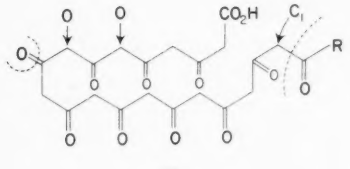
Concerning rutilantinone several experiments, not given here for reasons for brevity, have shown that base catalysed elimination of the alcoholic groups occurs easily thereby placing one of these hydroxyl groups β to the $-CO_2Me$. The other hydroxyl group was placed using biogenetic arguments giving structure (IV) for rutilantinone. These arguments utilize Birch's poly-β-keto acid precursor hypotheses and the oxygenation pattern in a precursor such as (V) does lead to (IV) for rutilantinone. The transformation (V ⟶ IV) involves biochemically and mechanistically reasonable processes including introduction of oxygen para to a potential or actual phenolic hydroxyl, introduction of a C_1 unit, loss of a -CO-R unit; the loss of phenolic oxygen is unexceptional.



IV

Rutilantinone

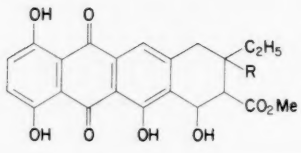


V

If these structures are correctly based, then (III) on oxidation could yield benzene-1,2,3,4-tetracarboxylic acid. Alkaline potassium permanganate oxidation of bisanhydrorutilantinone has in fact yielded this acid characterized as its tetramethyl ester, m.p. 130°, by comparison (m.p. and I.R. spectrum) with an authentic specimen. Thus structure (III)

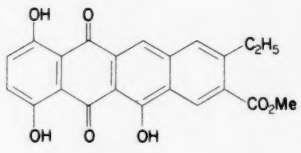
is confirmed.

Just after the completion of this work three papers appeared on the constitutions of some other antibiotics whose structures are remarkably similar to our structures for rutilantinone (IV) and bisanhydrorutilantinone (III). It has been shown that various Streptomyces strains have yielded ε-, ξ-, and η-pyrromycinones with the structures given below, and the glycoside, pyrromycin.[5,6,7]



VI

ε-Pyrromycinone, VIa; R=OH
ξ-Pyrromycinone, VIb; R=H



VII

η-Pyrromycinone

ε-Pyrromycinone (VIa) is isomeric with rutilantinone (IV) and η-pyrromycinone (VII) is isomeric with bisanhydrorutilantinone (III) and the same biogenetic precursor and transformations which have been indicated (see V) could give rise to all of them. It may be mentioned

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[5] L. Ettlinger, E. Gaumann, R. Hutten, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, P. Reusser and H. Zahner, J. Chem. Soc. 1867 (1959).

[6] H. Brockmann and W. Lenk, J. Chem. Soc. 1880 (1959).

[7] H. Brockmann and W. Lenk, J. Chem. Soc. 1904 (1959).

that our biogenetic arguments do differ significantly from those of Prelog, Brockmann and their collaborators, in that we suggest that the introduction of a C_1 unit involving a β-diketone structure (see V) might be more likely than terminal C-methylation or its equivalent. It would appear that an argument based on biogenesis has been important in the location of substituents in the pyrromycinone structures. The crucial experiment on η-pyrromycinone corresponding to our oxidation of bisanhydrorutilantinone to benzene-1,2,3,4-tetracarboxylic acid has not been reported.

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It is likely that the pyrromycinones and rutilantinones belong to a new group of antibiotics of common biosynthetic origin and just as pyrromycin, cinerubin A and cinerubin B are glycosides of ε-pyrromycinone (VIa), so the rutilantins are probably similarly derived from rutilantinone (IV).

We would like to acknowledge the help which we have received from the ultra-violet spectra given in two of Professor Brockmann's earlier publications.[3,8] We thank Professor W. Baker for his interest, and Mr. B. K. Kelly, The Director of the Antibiotic Research Station, Clevedon, and Dr. I. N. Asheshov for encouraging our collaboration.

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[8] H. Brockmann, L. Costa Pla and W. Lenk, Angew. Chem. 69, 477 (1957); H. Brockmann and W. Lenk, Ibid. 69, 477 (1957).

Tetrahedron Letters No. 16, pp.24-31, 1959. Pergamon Press Ltd. Printed in Great Britain.

ALLEGED S_N2 FINKELSTEIN SUBSTITUTIONS OF T-BUTYL BROMIDE[1]

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(Received 28 September 1959)

The relative reactivity of t-butyl halides in bimolecular nucleophilic substitution represents an important anchor point for our quantitative understanding of the subject,[2,3] and thus there is considerable interest in the recently reported rate constants for S_N2 reactions of t-butyl bromide with lithium bromide[4,5] and lithium chloride[6] in anhydrous acetone. These results are being widely quoted.[7] However, careful examination of the papers in question reveals that the S_N2 designation for these reactions was merely an assumption. In this Communication we show that the published experimental evidence and the results of further work by us make it clear that the reported rate constants do not correspond to the S_N2 mechanism.

The rates of the exchange reaction between t-butyl bromide and lithium

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[1] Research supported by the National Science Foundation.

[2] C. K. Ingold et al., J. Chem. Soc. 3200 (1955).

[3] C. K. Ingold, Quarterly Reviews 11, 1 (1957).

[4] L. J. LeRoux and E. R. Swart, J. Chem. Soc. 1475 (1955).

[5] P. B. de la Mare, ibid. 3180 (1955).

[6] E. D. Hughes, C. K. Ingold and J. D. H. Mackie, ibid. 3173 (1955).

[7] e.g., (a) A. Streitwieser, Jr., Chem. Reviews 56, 571 (1956); (b) E. Eliel, "Steric Effects in Organic Chemistry", John Wiley and Sons, New York, N. Y., 1956, p. 73; (c) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Henry Holt and Co., New York, N. Y., 1959, pp. 234-235, 274-276.

radio-bromide in acetone were treated by LeRoux and Swart with the aid of equation (1), the first and second terms on the right hand side of the

$$(R/a) = k_1 + k_2 [\alpha (LiBr)] \qquad (1)$$

$$(dx/dt)/(a-x) = k_1 + k_2 (b-x) \qquad (2)$$

equation representing unimolecular and bimolecular substitution, respectively. In the second term, the concentration of lithium bromide was multiplied by α, the degree of dissociation of the salt, in order to correct for the negligible reactivity of lithium bromide ion pairs compared to dissociated bromide ions.[8] The fit of the data by equation (1) was good, and at 40° unimolecular and bimolecular paths were judged to be of nearly equal importance at a lithium bromide concentration of 0.01 N. The bimolecular rate constant, k_2, was about one seventh that for isopropyl bromide.

In the work of the group at University College, London, on the reaction of t-butyl bromide with both lithium radio-bromide[5] and lithium chloride[6] in acetone, some disturbance from a unimolecular contribution was reported, but the main reactions were regarded as bimolecular substitutions. In the reaction with lithium radio-bromide a small amount of acid was observed and ascribed to the elimination component of the unimolecular reaction of t-butyl bromide. However, roughly second order kinetics were followed and second order rate constants were evaluated.

Although the treatment of t-butyl bromide with lithium chloride gave rise to more acid than does lithium bromide, Hughes, Ingold and Mackie[6] claim to have shown that the reaction is predominantly a substitution. There are disturbances from reversibility and other causes, which these workers hoped to avoid by confining the quantitative treatment of the

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[8] C. C. Evans and S. Sugden, J. Chem. Soc. 270 (1949).

measurements to the first 30-40% of the reaction. The specific rate of development of bromide ion, $[dx/dt)/(a-x)]$, was plotted against the concentration of chloride ion, $(b-x)$, according to equation (2), the intercept and slope supposedly giving k_1, the rate constant of the E1 reaction, and k_2, the S_N2 rate constant, respectively. At 55.20°, k_2 was reported to be 0.76×10^{-5} sec $^{-1}$ l. mole^{-1}, about one fifth the value for isopropyl bromide.

The main evidence for the S_N2 mechanism of reaction of t-butyl bromide offered by LeRoux and Swart[4] and Ingold and coworkers[5,6] was the observed kinetic form, and this is far from an unambiguous guide to mechanism. The use of equations such as (1) and (2) to separate unimolecular and bimolecular contributions involves the assumption that k_1 is insensitive to the salt concentration. This is known to be incorrect in acetone.[9,10c] The value of k_1 can be expected to increase with increased salt concentration in the approximately linear fashion reported by Salomaa[11] for alcoholysis of α-haloethers and by Winstein and coworkers[10] for ionization of various alkyl arenesulfonates and halides in acetic acid and other solvents including acetone.

An approximately linear pattern of salt effects in ionization reactions serves to make salt-promoted ionization take the same kinetic form

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[9] J. C. Charlton and E. D. Hughes, J. Chem. Soc. 2939 (1954).

[10] e.g., (a) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, J. Am. Chem. Soc. 76, 2597 (1954); Chemistry and Industry, 664 (1954); (b) A. H. Fainberg and S. Winstein, J. Am. Chem. Soc. 78, 2763 (1956); (c) S. Winstein, S. Smith and D. Darwish, ibid. in press.

[11] P. Salomaa, Ann. Univ. Turkuensis A114 (1953).

as bimolecular substitution. The ambiguity may be seen most clearly with equation (3), which shows how a linear pattern of acceleration of an ionization rate by a salt, MY, can be mistaken for contributing unimolecular and bimolecular contributions with rate constants k_1° and $k_1^\circ b$, respectively. Ingold and coworkers, who have actually reported salt effects which follow the linear pattern quite well in the case of chloromethyl ether in ether-alcohol[12] and t-butyl bromide in nitromethane[13] (Table I), failed to recognize this ambiguity.

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As summarized in Table I, the data on t-butyl bromide-lithium radio-bromide exchange are fit by equation (4) for an ionization reaction with a linear pattern of salt effects. In actual fact, equation (4) reproduces the first order rate constants of LeRoux and Swart[4] with just as low a

$$k_1 = k_1^\circ [1 + b\,(MY)] = k_1^\circ + k_1^\circ b\,(MY) \qquad (3)$$

$$R/a = k_1^\circ [1 + b\,(LiBr)] \qquad (4)$$

mean deviation as does equation (1). Since the rate constants reported by de la Mare[5] are in essential agreement with those of LeRoux and Swart, they also fit well to equation (4) (Table I). Obviously, kinetic form provides no argument for the S_N2 mechanism for the t-butyl bromide radio-bromide exchange.

With regards to the kinetics of the reaction of t-butyl bromide with lithium chloride, Hughes, Ingold and Mackie[6] report the actual data for one sample run at 55.20°, the concentration of t-butyl bromide being 0.1191 M and that of lithium chloride being 0.0634 M. Our own plot of the reported

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[12] P. Ballinger, P. B. D. de la Mare, G. Kohnstam and B. M. Prestt, J. Chem. Soc. 3641 (1955).

[13] P. B. D. de la Mare, E. D. Hughes, C. K. Ingold and Y. Pocker, ibid. 2930 (1954).

Table I

Reactions of t-Butyl Bromide in Various Solvents

Solvent	°C	Salt	$10^6 k_1^\circ$ sec^{-1}	b	Salt Range $10^2 M$	Ave. Fit % of k_1	Ref.
90% Me_2CO	50.0	$LiClO_4$	187	3.4	0-10	2.0	14
		LiBr	187	4.2	0-10		14
		LiCl	187	5.6	0-10		14
AcOH[a]	50.0	$LiClO_4$	79	13	0-3.4		14
$MeNO_2$	25.0	Et_4NCl	3.62	20.7	0.5-14	1.0	13
$HCONMe_2$	50.7	Et_4NBr	52	6.3	0-10		15
		NaBr	52	6.5	0-10		15
		Et_4NNO_3	52	3.2	0-17	2.4	15
Me_2CO	20.0[b]	LiBr	0.040	27.8	0.5-5	0.9	4
	40.0[b]	LiBr	0.38	27.4	0.5-10	4.7	4
	44.4[b]	LiBr	0.734	32.5	2.4-9	2.6	5
	60.0[b]	LiBr	2.46	29.0	0.5-5	4.8	4
	50.0	LiBr	1.23	33.8	0-8	7.8	
	50.0	$LiClO_4$	1.23	11.5	0-8	3.8	
	50.0	Bu_4NClO_4	1.23	12.2	0-8	5.5	
	50.0	LiCl	1.23	24	0-3		

[a] 0.068 M in LiOAc

[b] Radio-bromide exchange

$[(dx/dt)/(a-x)]$ values vs. $(b-x)$ according to equation (2) leads to a k_1 value of 1.8×10^{-6} sec^{-1} and a k_2 value of 7.6×10^{-5} sec^{-1} $l. mole^{-1}$, ten times the value reported by Hughes, Ingold and Mackie.[6] This new figure is twice the rate constant for isopropyl bromide.[6]

Ingold and coworkers[6] offered no evidence for S_N2 substitution based

[14] A. H. Fainberg and S. Smith, unpublished work.

[15] S. D. Ross and M. M. Labes, J. Am. Chem. Soc. 79, 4155 (1957).

on the nature of the products from the action of lithium chloride on t-butyl bromide. The reported acid titers for the one sample run corresponded to ca. 60% elimination, so that elimination was clearly more important than substitution. No direct evidence for formation of t-butyl chloride was obtained.

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In our own experiments on the behavior of t-butyl bromide in acetone, acid was observed to develop at a substantial rate initially, but the amount of acid tended to level off at a low value and then to rise again eventually as side reactions of the solvent occur and water develops. This behavior has been noted previously.[16] The addition of excess tetrabutylammonium chloride caused acid formation to be nearly quantitative, hydrogen chloride presumably being diverted as the bichloride salt. The addition of 2,6-lutidine tends to prevent loss of acid, nearly quantitative acid formation being observed in the absence or presence of lithium or tetrabutylammonium perchlorate, chloride or bromide. Vapor phase chromatographic analysis of aliquots of the reaction mixture showed (3 ± 1)% of t-butyl chloride was formed during runs with excess lithium or tetrabutylammonium chloride whether lutidine was present or not. Isobutylene was the major organic product, comparing favorably in amount with that of acid.

The rate of acid formation from t-butyl bromide in acetone was independent of lutidine concentration in the 0.02-0.09 M range. The first order rate constants were increased somewhat by addition of salt, the values at .03 M salt being compared in Table II. While the pattern of the variation of rate constant with salt concentration is not exactly the linear one, equation (3) fits the data fairly well, as is summarized in Table I for

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[16] L. C. Bateman, K. A. Cooper and E. D. Hughes, J. Chem. Soc. 913 (1940).

Table II

First Order Rate Constants at 50.0° for Acid Formation from t-Butyl Bromide in Acetone Containing 0.02 M 2,6-Lutidine and 0.03 M Salt

Salt	$10^6 k_1$ sec.$^{-1}$	Salt	$10^6 k_1$ sec.$^{-1}$
None	1.23	LiCl	2.11
$LiClO_4$	1.65	Bu_4NClO_4	1.78
LiCl	2.0[a]	LiBr	2.66

[a] Without lutidine

several of the salts.

Summing up the behavior of t-butyl bromide towards lithium chloride in acetone, it is clear that the reaction is nearly quantitatively elimination, only ca. 3% of the substitution product, t-butyl chloride, being formed. It would appear that Hughes, Ingold and Mackie[6] assumed not only the mechanism, but the reaction product as well. As regards the exchange reaction between t-butyl bromide, and lithium radio-bromide, it is significant that the initial rate of acid formation from t-butyl bromide in the presence of lithium bromide is approximately equal to the first order exchange rate. Further, the k_1° and b values from the exchange rates are nearly identical with those from the elimination rates (Table I), suggesting that exchange and elimination have the same rate-determining step. Very probably, exchange involves elimination and re-addition of hydrogen bromide, just as in nitromethane solvent.[13] The S_N2 designation is certainly unwarranted.

Except for a lower rate level, the behavior of t-butyl bromide towards bromide and chloride salts in acetone is exactly parallel to that in nitro-

methane, but Ingold and coworkers have somehow given quite different interpretations for the two solvents. The dependence of rates on salt concentration is not too different in the two solvents, judging by the b values in Table I, and yet the reaction of t-butyl bromide with tetraethylammonium chloride in nitromethane[13] has been labelled a unimolecular one, zero order in salt, and the reaction with lithium chloride in acetone[6] has been termed predominantly bimolecular substitution.

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While more needs to be known about ion pair return and salt effect patterns in acetone, and the mechanistic details of the proton removal, the most likely mechanism of elimination in acetone appears to be one involving initial ionization of the t-butyl bromide. As far as we now know, the sequence of relative rates and b values in the different solvents summarized in Table I are consistent with an ionization mechanism in acetone. The mechanism of formation of the very small amount of t-butyl chloride from t-butyl bromide is less clear.

The present change in the account of what is occurring when t-butyl bromide is treated with halide salts in acetone has a bearing on Ingold's quantitative treatment[2] of steric effects in S_N2 displacements. For the bimolecular Finkelstein reactions of methyl, ethyl and isopropyl bromides and the alleged bimolecular substitutions of t-butyl bromide, the energies of activation rise continuously with α-methyl substitution, while the entropy of activation decreases from methyl to isopropyl bromide and then rises again. This behavior of the entropy of activation was not associated with a change of mechanism. Instead, it was accounted for by a treatment[2] involving ponderal, steric and polar structural entropic effects, rates being fitted to within a small factor. This fit of the t-butyl bromide rates may no longer be regarded as support for the quantitative treatment.

Tetrahedron Letters No. 17, pp.1-6, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

STEREOCHEMISTRY OF AROMADENDRENE, ALLOAROMADENRENE, GLOBULOL, LEDOL AND VIRIDIFLOROL

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Czechoslovak Academy of Science, Prague

(Received 15 September 1959)

IN preceding papers of this series we proved the existence of a new hydrocarbon isomeric with aromadendrene which we called alloaromadendrene. Further, we elucidated the constitution of ledol and viridiflorol and their relationship to globulol and both isomeric aromadendrenes.[1-3] Recently, on the basis of degradation of aromadendrene, we established the location of the cyclopropane ring at compounds of this type.[4] In view of these results, both aromadendrenes are C_1 epimers of formula I, and ledol, viridiflorol and globulol C_1 and/or C_{10} epimers of structure II. Ledol and viridiflorol are derived from alloaromadendrene (the same configuration at C_1), globulol is related to aromadendrene.

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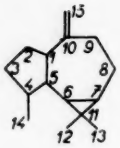
[1] L. Dolejš, M. Souček, M. Horák and F. Šorm, Chem. & Ind. 494 (1958); Chem. listy 52, 2189 (1958); Coll. Czech. Chem. Comm. 24, 1353 (1959).

[2] L. Dolejš, F. Šorm and M. Souček, Chem. & Ind. 160 (1959).

[3] L. Dolejš, V. Herout, O. Motl, F. Šorm and M. Souček, Chem. & Ind. 566 (1959); Coll. Czech. Chem. Comm. In press.

[4] L. Dolejš and F. Šorm, Tetrahedron Letters 10, 1 (1959).



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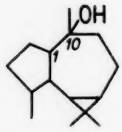

II

As Buchi et al.[5] published, a short time ago, complete structures of the discussed compounds, we also wish to report our present results which are in full agreement with those of the American authors.

On treatment with perphtalic acid, apoaromadendrone (III) afforded a lactone which on subsequent saponification yielded the hydroxy acid IV.[4] The keto-acid V (cf[6]), derived from the latter compound, on catalytical hydrogenation or on treatment with lithium tri-(t-butoxy)-aluminohydride converts into the isomeric hydroxy acid VI, m.p. 143.5°, $[\alpha]_D^{20}$ + 19.4° (methanol, c = 5.35). It may be assumed that the reagent approaches the carbonyl group of V from the side opposite to the bulky substituent in position α. Hence both hydroxy-acids may be allotted the configuration on C_1 and C_5 in the sense of formulae IV and VI respectively.

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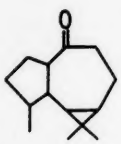
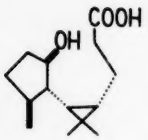
[5] G. Büchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard and M. Schach v. Wittenau, Tetrahedron Letters 6, 14 (1959).

[6] A. J. Birch and F. N. Lahey, Aust. J. Chem. 6, 379 (1953).

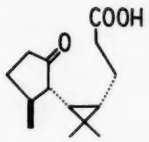
1959



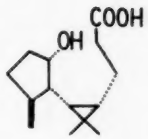
III



IV



V



VI

Further evidence of the configuration was obtained from the results of equilibration of both hydroxy-acids by aluminium isopropoxide at the presence of traces of the keto-acid V. Equilibration of the cis-derivative VI afforded a product which partially crystallized and from which the trans-acid IV was isolated; the acid IV, on the other hand, yielded a product which solidified completely, affording, after crystallization, only the unchanged starting material.

With regard to the above results and to the fact that the peracid-ketone reaction proceeds with retention of configuration of the migrating group,[7,8] the fusion of the five- and seven-membered ring in aromadendrene may be regarded as trans.

Birch and Lahey[6] elucidated the relative configuration of asymmetric

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[7] R. B. Turner, J. Amer. Chem. Soc. 72, 878 (1950).

[8] T. F. Gallagher and T. H. Kritchevsky, J. Amer. Chem. Soc. 72, 882 (1950).

carbon atoms C_4 and C_5 from the stability of the keto-acid V in alkaline medium. The configuration of centres of asymmetry of the cyclopropane ring in relationship to the other asymmetric carbon atoms may be deduced from the molecular models of ledol.

As has already been proved,[3] ledol possesses the opposite configuration on C_1 than aromadendrene; thus two alternative structures VII and VIII* with different orientation of the cyclopropane ring come into account for the former.** In the structure VIII, however, the five- and the seven-membered ring approach themselves to a considerable extent and strong interactions between the hydrogen atoms (at C_2, C_3, C_4) and the methyl group at C_{12} and the hydrogen atoms of the seven-membered ring (at C_8 and C_9) take place.

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* For structures VII and VIII R_1 = OH, R_2 = CH_3 or vice versa.

** The a priori possible pseudo-boat conformation of the seven-membered ring (IX) of structures VII and VIII may be, in both cases,

IX

excluded because of the total interference of the C_{10}-substituent (OH or CH_3) with the geminal-methyl group of the cyclopropane ring.

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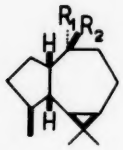
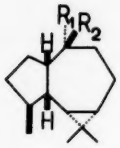
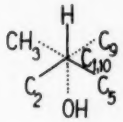


VII



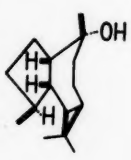
VIII

X

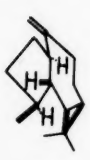


XI

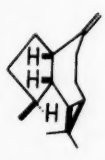
An unambiguous proof, excluding formula VIII, is constituted by the behaviour of ledol at dehydration. On treatment with thionyl chloride in pyridine, ledol afforded only a small amount of a hydrocarbon with a semicyclic double bond; the main product was an isomer with a quaternary double bond.[2] The almost uniform course of dehydratation requires a trans-antiparallel position of the eliminated hydrogen atom and the hydroxyl group. This condition is fulfilled in formula VII (R_1 = OH,



XII

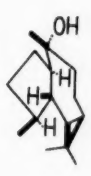


XIII



XIV

XV



XVI

$R_2 = CH_3$) only (cf. XI) contrary to the structure VIII (cf. X*). The resistance of ledol to form esters is also in agreement with the axial character of the hydroxyl group.

On the basis of the above discussed molecular models of ledol which is now formulated as XII, structures XIII and XIV follow for aromadendrene and alloaromadendrene and formula XV for the C_{10} epimer of ledol - the alcohol viridiflorol.[3] The configuration on C_1 in globulol corresponds to that in aromadendrene.[3] The former on dehydration with thionyl chloride in pyridine[2] affords 60 per cent yield of an olefin with a semicyclic double bond; this constitutes the proof of the equatorial character of the hydroxyl group as may be seen in formula XVI.

As the C_7 substituent at all hitherto known absolute configurations of sesquiterpenes and their derivatives is β-oriented[9] the submitted structures may be regarded tentatively as absolute configurations.

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* In projection X, R = OH or CH_3.

[9] D. H. R. Barton and J. E. D. Levisalles, J. Chem. Soc. 4518 (1958).

Tetrahedron Letters No. 17, pp.7-12, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

NOTE SUR LA REACTION ENTRE TRICHLORURE DE TITANE ET TRIMETHYLALUMINIUM

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(Received 21 September 1959)

A la suite des découvertes de Ziegler et de Natta, concernant la polymérisation des α-oléfines par des catalyseurs à base de dérivés organo-aluminiques et de tétra- ou trichlorure de titane, l'étude de la structure de ces catalyseurs a suscité un grand intérêt.[1-2]

Comme diverses expériences ont montré que la réaction entre tétrachlorure de titane et alkyl-aluminium fournit du trichlorure et qu'il est possible de former directement à partir de trichlorure de titane un catalyseur actif et plus stéréospécifique, il a paru plus intéressant d'étudier directement la structure du catalyseur formé par la réaction trichlorure de titane + alkyl - aluminium. D'autre part, en supprimant les solvants et en utilisant des réactifs aluminiques suffisamment volatils, on élimine les complications dues aux réactions sur les solvants

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[1] K. Ziegler, Brevet Belge, 533.362 et suivants.

[2] G. Natta, J. Pol. Sc. 16, 143 (1955); Angew. Chem. 213 (1957). Stereospezifische Katalysen und Isotaktische Polymere. Bad-Nauheim, Avril 1956.

et les difficultés de séparation des produits de réaction et des solvants.

La méthode d'étude utilisée a consisté à faire réagir les dérivés aluminiques, en quantités préalablement pesées, sur du trichlorure de titane, dans des appareils soigneusement vidés et excluant tout contact avec des graisses. Le trichlorure de titane était préparé par réduction au moyen d'hydrogène, de tétrachlorure de titane en phase vapeur passant sur des spirales de tungstène portées à 550°C; le trichlorure ainsi obtenu n'a jamais été au contact d'air et fut soigneusement débarrassé, sous vide et à 85°C, des dernières traces de tétrachlorure. Le triméthylaluminium a été préparé par la voie mercurielle.

Les réactions $TiCl_3$ + $AlMe_3$ donnent naissance à 2 types de produits: des produits volatils et des produits non-volatils que l'on peut aisément séparer.

Lorsque l'on met en contact $TiCl_3$ et $AlMe_3$ il se produit des gaz C_R (carbone de réaction); après un temps de réaction donné, ces gaz sont pompés ainsi que des liquides dont la faible tension de vapeur permet de les séparer des gaz C_R. Après pompage des gaz C_R et des liquides de faible volatilité, la phase non-volatile a été maintenue durant des temps variables à des températures choisies et il s'est produit alors des gaz C_D (gaz de décomposition). Les liquides de faible tension de vapeur sont ensuite pesés puis analysés par alcoolyse-hydrolyse pour déterminer leur teneur en groupes alkyles (gaz appelés C_v) et pour établir leur pourcentage en chlore (Cl_v) et en aluminium (Al_v). La différence entre l'aluminium initialement mis en réaction, déterminé par pesée et l'aluminium récupéré dans la phase volatile donne la quantité d'aluminium fixé (Al_{nv}) dans la phase non-volatile qui

constitue le catalyseur.

La phase non-volatile a été soumise à l'alcoolyse ou à l'hydrolyse et donne un gaz C_A (carbone d'alcoolyse) en plus de la solution alcoolique ou aqueuse.

Les données numeriques significatives sont rassemblees dans le tableau suivant:

Température de la réaction (°C)	65	65	65	65	65	85
Durée de la réaction	10'	120'	120'	120'	150'	60'
Température de la décomposition (°C)	65	65	65	65	22	85
Durée de la décomposition	162 h	60'	120'	100 h	66 h	60'
Conversion[a]	0.072	0.20	0.17	0.18	0.12	0.38
Cl_v/Al_{nv}	0.91	0.99	0.97	1.15	1.06	1.02
$(C_i-C_v)/Al_{nv}$[b]	3.9	4.0	4.0	4.1	4.1	4.0
$(C_R + C_D + C_A)/Al_{nv}$	2.8	4.0	4.0	3.45	4.0	4.1
x[c]	0.46	0.43	0.43	0.46	0.43	0.51

[a] La conversion de la réaction est définie comme rapport $Al_{nv}/Al_{initial}$ Tous les rapports sont des rapports molaires.

[b] C_i (carbone initial) représente les groupes méthyles du triméthyl-aluminium mis en réaction.

[c] x est defini par $(C_R + C_D)/(C_i-C_v)$.

Les gaz C_R comportent du methane et des traces d'éthane (2-3% en moyenne); les gaz C_D comportent exclusivement du méthane, de même que les gaz C_A pour leur partie organique. Pour les réactions à 65-85°C, pour des

temps de réaction et de décomposition courts (60-120') la quasi totalité (plus de 95%) du carbone entrant en réaction est récupérée sous la forme de méthane dans les gaz C_R, C_D et C_A. Aucune trace de polymère n'est décelable après alcoolyse ou hydrolyse de la phase non-volatile, même après les longues périodes de décomposition.

L'étude de ces résultats montre que, en ce qui concerne les réactions de faible durée, il faut exclure toute réaction de polymérisation et comme le gaz C_A n'est formé que de méthane, les groupes carbonés présents dans le catalyseur ne comportent chacun qu'un seul carbone; d'autre part, le rapport Cl_v/Al_{nv} voisin de 1 indique qu'il faut prévoir l'arrachement d'un atome de chlore du $TiCl_3$ par atome d'aluminium fixé; enfin, le rapport $C_i\text{-}C_v/Al_{nv}$ voisin de 4 fait penser que dans un premier stade de réaction quatre groupes méthyles sont fixés par atome d'aluminium lié sur le $TiCl_3$. Ces deux dernières caractéristiques suggèrent que la réaction met en jeu le dimère du triméthylaluminium, qui est d'ailleurs la forme prépondérante sous laquelle existe ce produit.[3]

Le schéma réactionnel suivant tient compte de ces données:

$$TiCl_3 + Al_2Me_6 \longrightarrow 1/2(AlClMe_2)_2 + [TiCl_2 \cdot {}_I\, AlMe_4] \qquad (1)$$

quoique, pour des raisons énergétiques, la réaction devrait sans doute être doublée pour recupérer les quelques 20 à 30 kcal/mole donnees par la dimérisation de $AlClMe_2$ en $Al_2Cl_2Me_4$.[3]

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[3] A. W. Laubengayer et W. F. Gilliam, J. Amer. Chem. Soc. 63, 477 (1941); R. H. Wiswall et C. R. Smyth, J. Chem. Phys. 9, 352 (1941); L. O. Brockway et N. R. Davidson, J. Amer. Chem. Soc. 63, 3287 (1941); P. H. Lewis et R. E. Rundle, J. Chem. Phys. 21, 986 (1953).

Le produit I, qui probablement se présente sous une forme ionisée:

$$[Ti^{+}Cl_2 \cdot Al^{-}Me_4]$$

se décompose ensuite comme le montre l'existence des gaz C_D, les groupes methyles donnant, pertiellement, du methane.

La réaction seconde peut s'écrire, en toute généralité:

$$[TiCl_2 \cdot AlMe_4] \longrightarrow 4x\ CH_4 + [TiCl_2 \cdot Al \cdot C_{4(1-x)}H_{4(3-4x)}] \quad (2)$$

Dans cette équation, le méthane correspond aux gaz dénommés C_R et C_D. La valeur de x (cf. note du tableau) croît avec le temps, et pour les températures utilisées, la variation de x, très rapide au debut et très lente par après, indique que deux types de réaction doivent s'effectuer: une première très rapide et une seconde beaucoup plus lente, qui devient la réaction principale quand les valeurs de x s'approchent de 0.5. D'autre part, lorsqu'on hydrolyse la phase non-volatile par D_2O, on obtient toujours (quoique les proportions varient selon les conditions de la réaction $AlMe_3$-$TiCl_3$)la gamme complète des méthanes CD_4 - CD_3H - CD_2H_2 - CDH_3 - CH_4. Ce résultat suggère que la phase non-volatile, qui est catalyseur efficace de la polymérisation de l'éthylène et du propène, ne comporte pas uniquement des groupements $-CH_3$ et $-CH_2-$ au sens de la chimie organique.[4]

Enfin, il faut insister sur le fait que les résultats quantitatifs mentionnés ne sont valables que dans la gamme des températures indiquées

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[4] Il y a lieu de comparer avec les conclusions, entre autres, de M. M. Wright et H. S. Taylor, Canad. J. Res. 27B 303 (1949).

et en absence de solvant. Toutefois, l'enlèvement de chlore du $TiCl_3$ est une caractéristique générale (de même pour les réactions avec $TiCl_2$) valable à toute température au dessus de $0^{\circ}C$, avec ou sans solvant, aussi bien pour le triméthyl- que pour le triéthylaluminium.

Ce travail a été effectué sous les auspices de l'Union Carbide Corporation, New York, N.Y.

Tetrahedron Letters No. 17, pp.13-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

HYDROXYFERROCENE

A. N. Nesmeyanov, V. A. Sazonova and V. N. Drozd

U.S.S.R. Academy of Sciences, Moscow

(Received 24 September 1959)

BENSON and LINDSEY[1] had synthesized bis-(1- hydroxy-3-methylcyclopentadienyl) iron by treating 3-methyl- 2 cyclopentenone in liquid ammonia with sodium amide and ferrous chloride.

We succeeded in preparing hydroxy ferrocene via ferrocenylboric acid.[2] The reaction of the latter with copper acetate resulted in ferrocenyl acetate (59 per cent yield) and biferrocenyl (21 per cent yield), the reaction with copper propionate taking the same course.

$$\varphi B(OH)_2 + 2Cu(OCOR)_2 + 2H_2O \rightarrow \varphi OCOR + 3RCOOH + Cu_2O + H_3BO_3$$

$$2\varphi B(OH)_2 + 2Cu(OCOR)_2 + 3H_2O \longrightarrow \varphi\text{-}\varphi + 4RCOOH + Cu_2O + 2H_3BO_3$$

with $R = CH_3$, C_2H_5; φ = ferrocenyl $C_5H_5FeC_5H_4$.

It is known from the literature[3] that phenylboric acid is oxidized by

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[1] R. E. Benson and R. V. Lindsey, J. Amer. Chem. Soc. 79, 5471 (1957).

[2] A. N. Nesmeyanov, V. A. Sazonova and V. N. Drozd, Dokl. Akad. Nauk S.S.S.R. 126, No. 5, 1004 (1959).

[3] Z. Holzbecher, Chem. listy 46, 17 (1952).

Compound	Formula	M.p. (°C)	Found			Calculated		
			C	H	Fe	C	H	Fe
1. Hydroxyferrocene	$C_5H_5FeC_5H_4OH$	166-170	59.48	5.06	27.60	59.45	4.99	27.65
2. Methoxyferrocene	$C_5H_5FeC_5H_4OCH_3$	39.5-40.5	61.18	5.81	25.44	61.14	5.60	25.85
3. Ferrocenyl acetate	$C_5H_5FeC_5H_4OCOCH_3$	64.5-66	59.00	4.98	22.80	59.03	4.96	22.88
4. Ferrocenyl propionate	$C_5H_5FeC_5H_4OCOC_2H_5$	30-31	60.40	5.66	21.61	60.50	5.47	21.64
5. Ferrocenyl benzoate	$C_5H_5FeC_5H_4OCOC_6H_5$	108.5-109.5	66.79	4.71	18.25	66.70	4.61	18.24
6. Ferrocenyl benzosulphonate	$C_5H_5FeC_5H_4OSO_2C_6H_5$	90-90.5	56.07	4.16	16.53	56.15	4.12	16.32

copper acetate to phenol, whereas O - and m - nitrophenylboric acids are oxidized to 2,2' and 3,3' -dinitrobiphenyl, respectively.

The structure of ferrocenyl acetate has been proved by its reaction with phenylmagnesium bromide.

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$$\varphi OCOCH_3 + 2C_6H_5Mg\,Br \longrightarrow \varphi OMg\,Br + (C_6H_5)_2\,\underset{\underset{OMg\,Br}{|}}{C} - CH_3$$

$$\varphi OH \xrightarrow[C_6H_5COCl]{NaOH} \varphi OCOC_6H_5$$

Hydroxyferrocene or ferrocenol can be isolated from alkaline solutions, just as phenol, by treatment with carbon dioxide. It is a yellow crystalline substance, decomposing within several days when exposed to air but stable in nitrogen; m.p. 166-170°C (in nitrogen).

Hydroxyferrocene has also been obtained by the hydrolysis of ferrocenyl acetate in alcohol-alkaline medium. Besides hydroxyferrocene the following derivatives have been synthesized.

Hydroxyferrocene is soluble in ether, alcohols, and chloroform, but insoluble in benzene; its esters are readily soluble in organic solvents. Other properties of hydroxyferrocene are being studied.

Tetrahedron Letters No. 17, pp.16-18, 1959. Pergamon Press Ltd. Printed in Great Britain.

REACTION OF ISOTHIOCYANATES AND IODINE PENTAFLUORIDE

Travis E. Stevens

Rohm & Haas Co., Redstone Arsenal Research Division

Huntsville, Alabama

(Received 29 September 1959)

A UNIQUE fluorination has been observed in the reaction of iodine pentafluoride and some alkyl and aryl isothiocyanates. This fluorination, when conducted in pyridine solution at 75-90°, has been found to produce a new class of compounds, the bis-(N-substituted-N-trifluoromethyl)-aminosulfides (I).

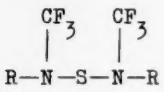
$$R{-}N{=}C{=}S + IF_5 \rightarrow (R{-}\overset{\displaystyle CF_3}{\underset{|}{N}}{-})_2{-}S$$

I

Table 1 lists the aminosulfides prepared in this way. The aromatic isothiocyanates were converted to the crude aminosulfides in almost quantitative yield,[1] however, recrystallization from ethanol or petroleum ether was necessary to obtain sharp-melting samples. Formulation

[1] No aminosulfide could be obtained from p-nitrophenyl, p-acetylphenyl, or p-dimethylaminophenyl isothiocyanates.

TABLE 1. bis-(N-Substituted-N-trifluoromethyl)-aminosulfides



R	M.P. (b.p.) (°C)	Yields (%)
Phenyl	53-54	19[a]
p-Fluorophenyl	32-33	34
p-Chlorophenyl	55-56	59
p-Bromophenyl	70-71	69
p-Iodophenyl	103-104	47[b]
m-Bromophenyl	(125°/0.5 mm)	90
p-Tolyl	58-59	40
Ethyl	(44°/30 mm)	33
Butyl	(80°/12 mm)	32

[a] The reaction product was a mixture of this and the p-iodo compound and the mixture was not separated completely.

[b] Also isolated from the phenyl isothiocyanate-iodine pentafluoride reaction.

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of these compounds as aminosulfides is based on the analytical data, n.m.r. spectra and hydrolytic experiments outlined below.

All compounds listed in Table 1 gave satisfactory analytical values,[2]

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[2] Data obtained by Dr. Keith S. McCallum.

for example, for bis-[N-(p-bromophenyl)-N-trifluoromethyl]-amino-sulfide was found C, 32.68; H, 1.76; N, 5.46; S, 6.59; F, 22.0; MW, 471.

The ^{19}F n.m.r. spectra of several of the aminosulfides were obtained using a Varian Associates model No. V-4300 B spectrometer with a 40 Mc probe.[2] Only a single peak, attributable to the CF_3 group, was observed; in compound I, R = p-bromophenyl, this fluorine resonance occurred at 927 c.p.s. lower field than trifluoroacetic acid, while when R = p-fluorophenyl resonance occurred at -892 c.p.s.,[3] and when R = n-butyl resonance at -760 c.p.s. was observed.

Hydrolysis of the aminosulfides I with aqueous ethanolic sodium hydroxide at room temperature for four hours resulted in the quantitative liberation of fluoride ion. The organic products of this hydrolysis in 75 per cent ethanol, in the case of I, R = p-bromophenyl, were p-bromoaniline (53 per cent) and p-bromophenylurethan (33 per cent). Similarly, I, R = p-chlorophenyl, yielded p-chloroaniline (51 per cent) and p-chlorophenyl-urethan (23 per cent). Hydrolysis with an ethanol-water-hydrochloric acid mixture gave the same products.

The aminosulfide I, R = p-bromophenyl, also was obtained (18 per cent yield) from the iodine pentafluoride-p-bromophenyl isonitrile-sulfur reaction. From the reaction of iodine pentafluoride, sulfur and N-n-butyl-formamide was obtained I, R = n-butyl (21 per cent).

Further details of this work will be reported later.

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[3] Resonance observed at + 1412 c.p.s. was due to the aromatic fluorine.

Tetrahedron Letters No. 17, pp. 19-22, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

LIGNANE DES LÄRCHEN- UND ERLENHOLZES
(Larix decidua und Alnus glutinosa)

K. Freudenberg und K. Weinges

Chemisches Institut der Universität und dem Forschungsinstitut für die Chemie des Holzes und der Polysaccharide, Heidelberg

(Received 5 October 1959)

AUS dem Ätherextrakt des Lärchenholzes (Larix decidua) lassen sich durch Gegenstromverteilung vier kristalline Verbindungen isolieren. Die Hauptmenge (ca. 70%) des Extraktes bilden Dihydro-quercetin (Taxifolin) und Dihydrokämpferol (Aromadendrin).[1] Neben den Dihydro-flavonolen kristallisiert eine Verbindung mit der Summenformel $C_{20}H_{24}O_7$ (ber. C 63.83 H 6.38 OCH_3 16.51 gef. C 64.03 H 6.44 OCH_3 16.51). Das Produkt ist mit dem von Freudenberg und Knof[2] aus Fichtenholz (Picea excelsa) isolierten Liovil (I) in Schmelzpunkt, spez. Drehung, R_f-Wert und I.R.-Spektrum identisch. Ein zweites Lignan mit der Summenformel $C_{20}H_{26}O_6$ (ber. C 66.35 H 7.25 O 26.52 OCH_3 17.15 gef. C 66.15 H 7.38 O 26.63 OCH_3 17.10) stimmt in Schmelzpunkt (113°) und spez. Drehung ($[\alpha]_D^{25}$ = -35°, Aceton, c=2)

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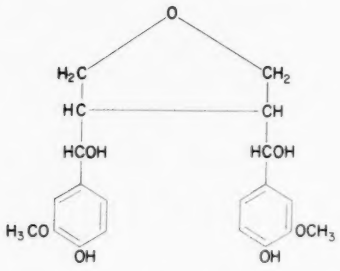
[1] J. Gripenberg, Acta Chem. Scand. 6, 1152 (1952).

[2] K. Freudenberg und L. Knof, Chem. Ber. 90, 2857 (1957).

mit dem von Briggs et al.[3] vor kurzem beschriebenen Seco-iso-lariciresinol (II) überein. Die Strukturformel wurde von obigen Autoren durch $LiAlH_4$-Reduktion des (-)-Matairesinols bewiesen.



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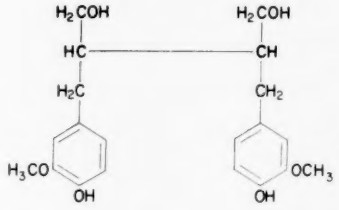

II

Ein neues Lignan-glykosid mit der Summenformel $C_{27}H_{36}O_{12}$ (ber. C 58.74 H 6.57 OCH_3 22.49 gef. C 58.75 H 6.63 OCH_3 22.50; Schmp. 122-124°; $[\alpha]_D^{25}$ = +38° Aceton/Wasser 1:1, c=2) konnte in 0.01 %iger Ausbeute (bezogen auf das Holzmehl) aus dem Essigesterextrakt des Erlenholzes (Alnus glutinosa) kristallin isoliert werden. Durch Kochen mit 1 %iger Schwefelsäure erhält man das Dimethoxy-iso-lariciresinol (III) (ber. C 62.91 H 6.72 OCH_3 29.56 gef. C 62.52 H 6.92 OCH_3 29.33; Schmp. 165-167°; $[\alpha]_D^{25}$ = +52° Aceton, c=2). Als Zucker wurde papier-

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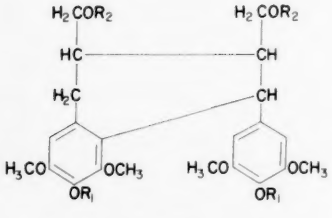
[3] L. H. Briggs, R. C. Cambie und J. L. Hoare, Tetrahedron Letters No. 4, 14 (1959).

chromatographisch Xylose nachgewiesen.

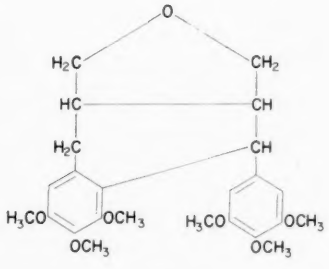
In der folgenden Tabelle sind die Schmelzpunkte einiger Derivate des Dimethoxy-iso-lariciresinols angeführt.

Derivat	Schmp.
Dimethyl-dimethoxy-iso-lariciresinol (IV)	152-152°
Dimethyl-diacetyl-dimethoxy-iso-lariciresinol (V)	88-89°
Tetraacetyl-dimethoxy-iso-lariciresinol (VI)	157-159°
Anhydro-dimethyl-dimethoxy-iso-lariciresinol (VII)	136-137°

Das Anhydro-dimethyl-dimethoxy-iso-lariciresinol (VII) wird aus Produkt IV mit $KHSO_4$ bei 180° erhalten.



III R_1 und R_2 = H
IV R_1 = CH_3; R_2 = H
V R_1 = CH_3; R_2 = $COCH_3$
VI R_1 und R_2 = $COCH_3$



VII

Der Extrakt enthält noch zwei weitere Glykoside, deren Trennung bisher nicht gelungen ist. Lässt man auf das Glykosidgemisch Emulsin einwirken, so wird das eine der Glykoside gespalten; sein Aglykon wird mit Methylenchlorid ausgeschüttelt und aus Wasser umkristallisiert. Das Aglykon hat die Summenformel $C_{24}H_{28}O_5$ (ber. C 72.79 H 7.13 Molgew. 396, gef. C 72.62; 72.87; 72.78 H 7.25; 7.28; 7.29 Molgew. 409; Schmp. 126-128°). Sein I.R.-Spektrum zeigt eine Carbonylgruppe an. Als Zucker wurde papierchromatographisch Glucose nachgewiesen.

1959

Tetrahedron Letters No. 18, pp.1-4, 1959. Pergamon Press Ltd. Printed in Great Britain.

DIRECT CORRELATION OF ACONITINE AND DELPHININE

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(Received 13 October 1959)

1959

Some time ago complete structures for aconitine I[1] and delphinine II[2] have been deduced. In these structures the only ambiguity was the fact that the methoxyl in ring A and the group R_2 could possibly be exchanged in position.

This ambiguity was now removed for aconitine by chemical studies[3] and also X-ray crystallography.[4] Consequently, the formula I for aconitine is fully established.

It was considered probable that delphinine had the same orientation of the ring A methoxyl corresponding to the formula II, and that this fact would be most conveniently established by direct correlation of aconitine and delphinine. Such a correlation would have the additional advantage of reinforcing the structural arguments for both compounds.

After several unsuccessful attempts, the desired correlation was accomplished by a conversion of aconitine into the aromatic compound VIII, which has previously been obtained from delphinine[1].

Pyrooxonitine[1] was reduced by means of sodium borohydride in methanol and the product was directly

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[1] K. Wiesner, M. Gotz, D. L. Simmons and L. R. Fowler; F. W. Bachelor, R. F. C. Brown and G. Buchi, Tetrahedron Letters No. 2, 15 (1959).

[2] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Gotz, Tetrahedron Letters No. 3, 11 (1959).

[3] G. Buchi, Private Communication

[4] M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).

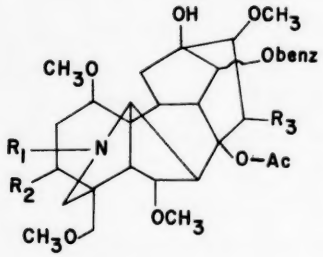
saponified by refluxing with aqueous ethanolic potassium hydroxide. The amorphous dihydropyrooxonine III was continuously extracted with chloroform and purified by chromatography on silicic acid. The infrared spectrum of III showed a single peak in the carbonyl region at 1655 cm^{-1} which belongs to the N-acetyl group.

Compound III took up one mole of periodic acid and the amorphous product IV was immediately aromatized by heating under extreme dilution in 0.01m ethanolic potassium hydroxide in a current of oxygen to 60-65°. After acidification and continuous extraction with chloroform, the products of the aromatization were separated by chromatography on silicic acid. The desired product V, which is distinguished by a characteristic p-hydroxyacetophenone spectrum, was obtained as a spectroscopically pure, but amorphous, white foam. Ultraviolet spectrum: (0.01m KOH in ethanol) λ_{max} = 337 mμ (log ε=4.13), shoulder 248 mμ (log ε=4.00); (0.01m H_2SO_4 in ethanol) λ_{max} = 286 mμ (log ε=3.9), λ_{max} = 231 mμ (log ε=4.0). Infrared spectrum: 1668 cm^{-1}, 1600 cm^{-1}, 1575 cm^{-1}.

The phenol V was converted into the methyl ether VI by treatment with ethereal diazomethane.

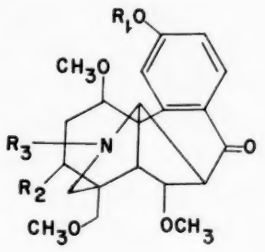
Compound VI was purified by chromatography on alumina and remained oily. Ultraviolet spectrum in ethanol: λ_{max} = 280 mμ (log ε=3.8), 229 mμ (log ε=3.9). Compound VI was heated for 1 hour with an excess of dichlorophenylphosphine oxide to 115° and the chloroderivative VII was purified by chromatography on Florisil. It had an ultraviolet spectrum identical with compound VI and the infrared spectra of VI and VII were practically identical except for the absence of an OH peak in VII. Also, compound VII remained oily in spite of repeated chromatography and apparent spectroscopic purity. However, it was possible to convert VII readily into the crystalline compound VIII which has previously been obtained[1] from delphinine.

1959



I (R_1 = $-CH_2-CH_3$, R_2 = OH, R_3 = OH)

II (R_1 = $-CH_3$, R_2 = H, R_3 = H)

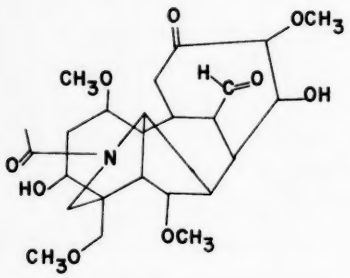


V (R_1 = H, R_2 = OH, R_3 = CH_3-CO-)

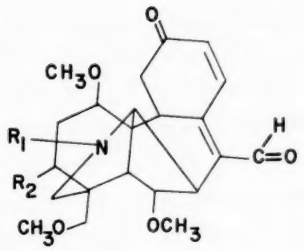
VI (R_1 = $-CH_3$, R_2 = OH, R_3 = CH_3-CO-)

VII (R_1 = $-CH_3$, R_2 = Cl, R_3 = CH_3-CO-)

VIII (R_1 = CH_3, R_2 = R_3 = H)

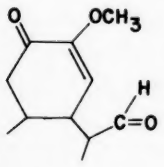


IV

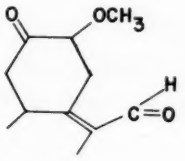


IX (R_1 = $C(=O)H$, R_2 = H)

X (R_1 = CH_3-CO-, R_2 = $-OH$)



XI



XII

To this end, compound VII was first refluxed with glacial acetic acid and zinc dust, and the crude product of this reaction was again refluxed with methanolic hydrochloric acid. The product of this last reaction VIII was basic and it was purified by chromatography on alumina followed by crystallization of the highly insoluble oxalate. The oxalate reached a constant melting point of 194°, and showed no melting point depression with the corresponding derivative VIII prepared from delphinine. Decomposition of the oxalate gave base VIII, m.p. 144°, which did not show melting point depression with VIII, m.p. 144°, obtained from delphinine. Also the infrared and ultraviolet spectra of both samples were identical.

It has been postulated previously[1] that the aromatization of the secoketoaldehyde from α-oxoisopyro-delphonine proceeds via the intermediate IX. The analogous intermediate X may be obtained from the secoketoaldehyde IV in a series of base catalyzed reactions proceeding via the intermediates XI and XII portrayed by partial structures. The precise mechanism of the aromatization reactions will be discussed in a full communication on aconitine chemistry.

Two points of special significance of the present correlation should be emphasized. This is the already-mentioned rigorous location of the ring A methoxyl in delphinine and the rigorous location of the ring B methoxyl in aconitine at C_6. This group was previously placed in aconitine[1] only by analogy, but rigorous evidence exists for its location in delphinine chemistry.[2]

Tetrahedron Letters No. 18, pp.5-6, 1959. Pergamon Press Ltd. Printed in Great Britain.

DIE SYNTHESE VON 2,2'-HYDRAZO-DIPHENYLMETHAN.

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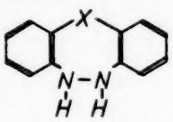
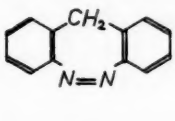
Institut für organische Chemie der Technischen Hochschule Hannover.

(Received 19 October 1959)

N.L. Allinger und G.A. Youngdale haben in den Tetrahedron Letters No.9, Seite 10-12, 1959 über die Synthese von Verbindungen des Typs I berichtet. Wir haben das 2,2'-Hydrazo-



I



II

diphenylmethan (I,X = CH_2) dargestellt, eine Verbindung die H.Duval[1] vergeblich zu erhalten versuchte. 4,4'-Diamino-diphenylmethan wird nach P. Ehrlich und H. Bauer[2] zu 2,2'-Dinitro-4,4'-diamino-diphenylmethan (III) nitriert. Die Desaminierung von III zu 2,2'-Dinitro-diphenylmethan (IV) ist von K. Schnitzspahn[3] und W. Bertram[4] beschrieben worden, das von ihnen erhaltene Produkt vom F. 159° ist aber kein 2,2'-Di-

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[1] H. Duval, Bull. Soc. Chim. Fr. (4) 7, 527 (1910).

[2] P. Ehrlich und H. Bauer, Ber. Dtsch. Chem. Ges. 48, 505 (1915).

[3] K. Schnitzspahn, J. Prakt. Chem. (2) 65, 315 (1902).

[4] W. Bertram, J. Prakt. Chem. (2) 65, 327 (1902).

nitro-diphenylmethan. Man kann IV jedoch in 40%iger Ausbeute erhalten, wenn man III in 50%iger unterphosphoriger Säure in Gegenwart von Kupfer(I)-oxyd diazotiert.[5] IV schmilzt bei 83,5° (Ber. für $C_{13}H_{10}O_4N_2$ C 60,5 H 3,9 N 10,9, gef.C 60,3 H 3,9 N 10,8) und bildet bei der Oxydation mit Chromsäure 2,2'-Dinitrobenzophenon. Katalytische Reduktion gibt 2,2'-Diaminodiphenylmethan (V) vom F. 134-135° (Acetylderivat F.198°), Reduktion mit Lithiumaluminiumhydrid liefert 2,2'-Azodiphenylmethan (II) in 41%iger Ausbeute. II kristallisiert in orangen Blättchen vom F. 109-110° (Ber.für $C_{13}H_{10}N_2$ N 14,4, gef. N 14,5) und löst sich in starker Salzsäure. II gibt in verd. Alkohol mit Ammoniak und Zinkstaub in 70%iger Ausbeute farbloses 2,2'-Hydrazo-diphenylmethan (I,X = CH_2) vom F.101-102° (Ber. für $C_{13}H_{12}N_2$ C 79,6 H 6,2 N 14,3, gef. C 79,5 H 6,2 N 14,3). I(X = CH_2) lagert sich mit Salzsäure in Stickstoffatmosphäre fast quantitativ in ein Gemisch von gleichen Teilen II und V um, Acridin[1] entsteht nicht.

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[5] D. C. Iffland und H. Siegel, J. Amer. Chem. Soc. 80, 1947 (1958).

Tetrahedron Letters No. 18, pp.7-10, 1959. Pergamon Press Ltd. Printed in Great Britain.

CYCLIC ETHERS FROM THE SELF-CONDENSATION OF 4,6-DIMETHYLOL-m-XYLENE

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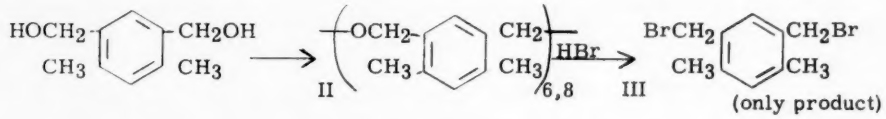
Union Carbide Plastics Company, Division of Union Carbide Corporation
Bound Brook, New Jersey

1959

(Received 2 October 1959)

ACID-CATALYZED condensations of dimethylolbenzenes generally lead to the expected hydroxy-ended linear polyethers. While such reactions for para-dimethylolbenzenes are detailed by Rhoad and Flory[1], they noted briefly that some meta-analogs also condense in this way. During the course of similar study, but with 4,6-dimethylol-m-xylene (I) and greater catalyst concentration, we detected no linear polyether of this type in the final product, but, instead, observed the quantitative formation of compounds whose characteristics are best represented by the cyclic poly (xylylene ether) (II). Molecular weight determinations indicated that, in separate experiments, the product isolated consisted of 6 and 8 monomeric units, respectively. Similar cyclic structures have not been previously reported.



4,6-Dimethylol-m-xylene, I, ($C_{10}H_{14}O_2$, m.p. 150-151°) was prepared by the method of v. Braun and Nelles[2]. It was heated, under N_2, with 1% by

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[1] M. J. Rhoad and P. J. Flory, J. Amer. Chem. Soc. 72, 2216 (1950).
[2] J. v. Braun and J. Nelles, Ber. 67, 1094 (1934).

weight of sulfamic acid at 200° for 0.5 hour. In each of the three successive experiments, the weight loss exactly equaled that had one mole of water been lost per mole of I. In each case the white product failed to exhibit hydroxyl function, in microchemical[3] and I.R. analyses. The products were purified through separation from xylene solution by the addition of methanol.

Expt. No.	Determinations on the Purified Products: M.P.[a]	M.W.[e]	Analysis, %[e]: C	H	O[b]
1	135.7-136.6°	890[c], 885[d], av. 888	81.04	8.04	10.92
			81.16	8.19	10.65
2	135.3-136.4°	882[c], 903[d], av. 893	81.24	8.21	10.55
			81.20	8.26	10.55
3	136-137°	1204[c], 1092[c], av. 1148	81.14	8.20	10.66
			81.22	8.03	10.75

[a] All melting points corrected; [b] % O, by difference; [c] Signer-Barger method; [d] Rast method; [e] Schwarzkopf Microanalytical Lab., Woodside 77, New York, M.W. accuracy within 5-10%.

Calculated from the analytical data, the empirical formula in each instance is $C_{10}H_{12}O$, exactly one H_2O less than the original diol (I) ($C_{10}H_{14}O_2$); This confirms the experimentally-observed weight loss. Structure II has the identical empirical formula, $C_{10}H_{12}O$: its 6-membered cycle has a calculated m.w. (888) comparing well with the determined values of products from experiments 1 and 2. The 8-membered cycle has a m.w. (1184) differing by only 3% from the average m.w. determined on the product from experiment 3.

The possibility of methylene-bridged functions, observed in small amounts in the self-condensation of p-xylylene glycol[1], was precluded in our case by the isolation of a single product, 4,6-bis-(bromomethyl)-m-xylene (III), m.p. 110-111° (lit. val.[2], 111°), by treatment of these isolated products with 48% HBr. Structure II would behave exactly this way.

[3] F. Feigl, Spot Tests in Organic Analysis, Elsevier, N.Y., 5th Ed. (1956).

It is interesting to note that we did isolate a product containing, apparently, some methylene-bridged cross-links, by the self-condensation of dimethylol-mesitylene with 1% sulfamic acid. The product, m.p.265-270°, was so appraised by it insolubility in aromatic solvents. Rhoad & Flory, employing .1% sulfamic acid in an otherwise identical reaction, obtained a composition, m.p.245-250°, that was soluble in phenylcyclohexane, and which was considered solely a linear polyether. The ten-fold difference in catalyst concentration could account for this variance.

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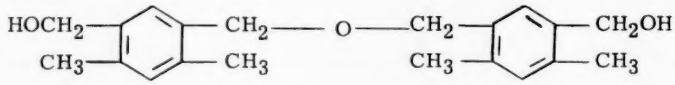
Further evidence for the cyclic nature of these condensation products is to be found in comparative melting points. It is seen that the melting points are quite sharp and are considerably lower than that of the starting diol (I). The sharpness is indicative of the relative purity and single nature of the product, while the lower melting point is significant of the absence of hydroxy function. On the other hand, the linear polyethers reported by Rhoad & Flory increased in melting point with increasing degree of polymerization, the melting points in all cases being higher than that of starting diol. This is quite consistent with their assignment of hydroxyl end-groups to these polymers.

It may be noted, finally, that, owing to the limited solubility of the linear polyethers, their molecular weights could not be determined by conventional means[1]. As reported, their degrees of polymerization were estimated from their carbon analyses, the starting monomer having the minimum % C, and the latter increasing with degree of polymerization to the maximum at infinite chain length. The only other condition of maximum % C is that justified by a cyclic polyether. Since our products were sufficiently soluble, conventionally determined m.w.'s (by Signer-Barger & Rast methods) were obtained and from them the degrees of polymerization, 6 and 8, as discussed, were calculated. The % C determined in each case was the maximum possible (equal to that calculated for infinite linear- or cyclic-structure). This, together with m.w., lack of hydroxyl

function, low m.p. and high solubility, affords considerable validity to the cyclic structure (II) that we have assigned to these products.

In another experiment employing I with .1% sulfamic acid, as the only variation, the observed weight loss was equivalent to the loss of one-half mole of water per mole of I. Here hydroxyl groups were positively identified. While the product was not further characterized, structure IV seems to correlate most aptly with these observations.

IV 

On the assumption that this dimer (IV) is the correct structure resulting from the use of .1% catalyst, it might be proposed that m-diols, such as I, react in pairs and, under the influence of more vigorous catalysis (1% sulfamic acid), these pairs then react to form the proposed cyclic systems. By the use of Stuart and Briegleb molecular models, we have found that the 6-unit cyclic structure is the smallest of this homologous series in which complete freedom of rotation is possible for each substituent group. The 8-unit structure is likewise stable. Since rings larger than these should have at least as much steric freedom, it does not seem probable that larger rings first formed and disproportionated into the 6- and 8-unit structures; if such disproportionations were to occur, the 6- and 8-unit cyclic ethers would also be subject to such, forming larger rings - which were not observed. This absence might also preclude a random, heterogeneous condensation. The possibility of sequential linear build-up, i.e., polymer reacting only with monomer, might also be ruled out since the sterically-stable 7-unit cycle should also be formed; it has not been found. (The 5-10% accuracy of the m.w. determinations, however, limits the validity of its absence.)

Tetrahedron Letters No. 18, pp. 11-13, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

ÜBER DIE IDENTITÄT DES MINORINS UND DES VINCAMINS[+]

Z. Čekan, J. Trojánek und E. S. Zabolotnaja[++]

Forschungsinstitut für Heilpflanzen, Prag

(Received 26 October 1959)

IM Jahre 1950 entdeckte einer von uns (E.S.Z.) in der Alkaloidfraktion des Immergrüns (Vinca minor L.) das Alkaloid Minorin[1] mit der Formel $C_{22}H_{26}N_2O_3$, Schmp. 223 - 224° (Zers.), $[\alpha]_D$ -8,4° in Chloroform. Sechs Jahre später wurde von Junusow, Juldaschew und Plechanowa[2] die Anwesenheit dieses Alkaloids in Vinca erecta Rgl. et Schmalh. festgestellt und seine Formel auf Grund neuer analytischen Daten auf $C_{22}H_{28}N_2O_3$ berichtigt. Unabhängig von der Arbeit der E.S.Z.[1] isolierten im Jahre 1953 Schlittler und Furlenmeier[3] aus Vinca minor L. das Alkaloid Vincamin mit dem Schmp. 232 - 233° (Zers.) und $[\alpha]_D^{23}$ +41° ± 4° (in Pyridin) und sprachen ihm auf Grund der analytischen Daten der freien Base sowie des Pikrats die Summenformel $C_{21}H_{26}N_2O_3$ zu. Die Existenz des Vincamins in Vinca minor L. wurde später mehrmals

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[+] Es wurde teilweise am XIX. Internationalen Kongress der pharmazeutischen Wissenschaften in Zürich (September 1959) vorgetragen.

[++] E.S. Zabolotnaja, Allunions-Forschungsinstitut für Heil- und aromatische Pflanzen, Moskau.

[1] E. S. Zabolotnaja, Trudy Vsesojuznowo Nautschno-issledowatelskowo Instituta Lekarstwennych Rastenij (Moskau) No. X, 29 (1950).

[2] S.J. Junusow, P. Juldaschew und N.V. Plechanowa, Dokl. Akad. Nauk Uzb. SSR No. 7, 13 (1956).

von verschiedenen Autoren[4-7] bewiesen und die von schweizerischen Autoren[3] vorgeschlagene Formel bestätigt. Endlich wurde das Vincamin auch in Vinca difformis Pourr. von Janot und Mitarbeitern[8] aufgefunden.

Beim Studium des Verhaltens des Minorins und Vincamins bei der Papierchromatographie (mobile Phase Benzol-Cyklohexan 2:1, stationäre Phase Formamid)[9] stellten wir fest, dass beide Alkaloide die gleichen R_f-Werte (0,44) aufwiesen. Durch diese Übereinstimmung gelangten wir zu der Ansicht, dass das Minorin mit Vincamin identisch sein könnte, was durch weiteren Vergleich der Eigenschaften beider Naturstoffe volkommen bestätigt werden konnte.

Der Schmelzpunkt des Minorins, der auf dem Kofler-Block mit Genauigkeit $\pm 2^\circ$ ermittelt wurde, liegt bei 228 - 229,5° (Zers.), der des Vincamins[6] bei 232 - 233,5° (Zers.). Das Gemisch beider Alkaloide schmolz ohne Depression bei 229 - 230° (Zers.).

Das spezifische Drehvermögen des Minorins in Pyridinlösung ist, wie wir nun gefunden haben, $[\alpha]_D^{21}$ +39,5° $\pm 2^\circ$, was mit den publizierten Daten des Vincamins[3,4,6] in guter Übereinstimmung ist.

Die Infrarotspektren beider Alkaloide, welche mittels des IKS-14-Geräts in Paraffinölemulsion gemessen wurden, sind im Wesentlichen identisch

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3 E. Schlittler und A. Furlenmeier, Helv. Chim. Acta 36, 2017 (1953).

4 M. Pailer und L. Belohlav, Monatsh. 85, 1055 (1954).

5 F. E. King, J. H. Gilks und M. W. Partridge, J. Chem. Soc. 4206 (1955).

6 J. Trojánek, J. Hoffmannová, O. Štrouf und Z. Čekan, Coll. Czech. Chem. Comm. 24, 526 (1959).

7 K. Szász, L. Szporny, E. Bittner, I. Gyenes, E. Hável und I. Magó, Magyar Kémiai Folyóirat 64, 296 (1958).

8 M.-M. Janot, J. LeMen und C. Fan, Ann. Pharm. Fr. 15, 513 (1957).

9 J. Trojánek, K. Kavková, O. Štrouf und Z. Čekan, bisher nicht publiziert.

und stimmen mit den Werten, die für das Vincamin veröffentlicht wurden,[3,4] überein.

Die früher gefundenen Werte der Elementaranalyse des Minorins[1] (71,33; 71,45 %C, 7,52 %H, 7,59; 7,76 %N) stimmen mit den für Vincamin $C_{21}H_{26}N_2O_3$ berechneten Werten (71,16 %C, 7,39 %H, 7,90 %N) besser überein, als mit der Summenformel $C_{22}H_{26}N_2O_3$ (72,10 %C, 7,15 %H, 7,65 %N) oder $C_{22}H_{28}N_2O_3$ (71,71 %C, 7,66 %H, 7,60 %N).

Die Übereinstimmung der Eigenschaften des Minorins und des Vincamins betreffs ihrer Kristallformen, ihrer Löslichkeit in verschiedenen Lösungsmitteln,[1,4] der optischen Drehung, der papierchromatographischen R_f-Werte sowie ihrer Schmelzpunkte und I.R.-Spektren beweist ganz überzeugend die Identität beider Alkaloide.

Für die Durchführung der papierchromatographischen Analyse sind wir Frau Ing. K. Kavková aus dem Forschungsinstitut für Heilpflanzen, Prag, verbunden, für die Bemessung der I.R.-Spektren danken wir Dr. J. N. Scheinker aus dem Allunions-Forschungsinstitut für Chemie und Pharmazie, Moskau, herzlichst.

Tetrahedron Letters No. 18, pp. 14-16, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE BIOGENESIS OF ASPIDOSPERMINE

Robert Robinson

Shell Chemical Co. Ltd., 170 Piccadilly, London, W. 1.

(Received 14 October 1959)

INSPECTION of the molecular structure of aspidospermine recently disclosed[1] allows of the recognition of an interesting biogenesis sequence which raises important side-issues.

Strychnine and vomicine (which contains a methoxyl group in the same position as in aspidospermine) are almost certainly derived from a tryptamine (or substituted tryptamine) residue (or equivalent) condensed with a tyrosine or dihydroxyphenylalanine moiety, modified by the Woodward fission[2] together with a so-called berberine-bridge carbon atom and a molecule of acetic acid (or equivalent). The side chain of the phenylalanine derivative is degraded to $R.CH_2CO.CO_2H$ or $R.CH_2.CHO$ and this carbonyl becomes attached to the 3- (or β-) position of the indole ring. The (B) carbon atom connects the tryptamine nitrogen to a position (originally - CH =) of the benzene ring of the phenylalanine. The aspidospermine skeleton may be

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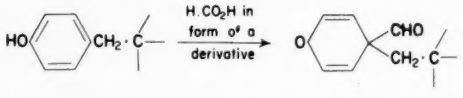
[1] Mills and Nyburg, Tetrahedron Letters, No. 11, 1 (1959); Conroy, Brook and Amiel, Ibid, No. 11, 4 (1959).

[2] Woodward, Nature, Lond. 162, 155 (1948).

derived from the same starting points but the positions of condensation are different.

The CHO (or $CO.CO_2H$) of the degraded phenylalanine derivative side-chain becomes connected with the 2- (or α-) position of the tryptamine nucleus and the (B) carbon becomes attached to the 3- (or β-) position of the indole nucleus, also to the tryptamine basic N atom and, probably most significantly, to that carbon of the substituted phenylalanine progenitor which is p to the hydroxyl of tyrosine. Reduction, closure of the piperidine ring, and acetylation complete the necessary processes.

The bifurcation which leads to aspidospermine may well be conceived as connected with the mode of introduction of the (B) carbon. This is plausibly derived from formic acid (in suitable combination) and with formation of a hydro-aromatic type represented below as if from tyrosine, merely for purposes of illustration.



If this almost necessary hypothesis is approved it would strongly indicate the origin of aspidospermine from a true aromatic phenylalanine derivative.

By analogy it can be inferred that the original hypothesis of Woodward in regard to the amino-acid progenitors of strychnine (and other indole alkaloids) is strengthened. It seems very probable that these are both

benzenoid and that alicyclic intermediates (Wenkert) are not concerned in the process apart from modifications of the aromatic nuclei (as above for example) and naturally in the synthesis of the aromatic nuclei of the amino-acids themselves.

On the other hand it is an obvious possibility that the 1-carboxyl of prephenic acid (Davis, Sprinson) provides the (B) carbon atom in question. Nevertheless this attractive suggestion raises other difficulties, which require more detailed discussion than is possible in this place.

A private communication from Dr. W. I. Taylor, discloses that alkaloids of Hunteria Eburnea Pichon possess the same skeleton as aspidospermine and the suggested biogenesis obviously also applies to these substances.

Tetrahedron Letters No. 18, pp. 17-19, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

TRANSFORMATION OF REICHSTEIN'S SUBSTANCE S TO PREDNISOLONE BY PSEUDOMONAS

Rokuro Takeda, Itaru Nakanishi, Jiro Terumichi,* Minoru Uchida, Michio Katsumata, Masao Uchibayashi and Hayao Nawa

Research Laboratories, Takeda Pharmaceutical Industries, Osaka, Japan

(Received 13 October 1959)

WE have reported previously[1] the microbiological conversion of Reichstein's Substance S (I) by Pseudomonas species into 1,4-pregnadiene-17α,20β,21-triol-3-one (II), hydrocortisone, 1,4-pregnadiene-17α,21-diol-3,20-dione and 4-pregnene-17α,20β,21-triol-3-one, thus disclosing the enzyme systems responsible for the three reactions, i.e. 1-dehydrogenation, 11β-hydroxylation and 20β-hydrogenation, to be present in the Pseudomonas species. From these findings the possibility was naturally anticipated that both the 1-dehydrogenation and the 11β-hydroxylation could be induced simultaneously in the same molecule of the substrate if the conditions for enzyme formation and for steroid transformation were properly selected. We now wish to record the successful microbial preparation of prednisolone from I, the realization of our anticipation.

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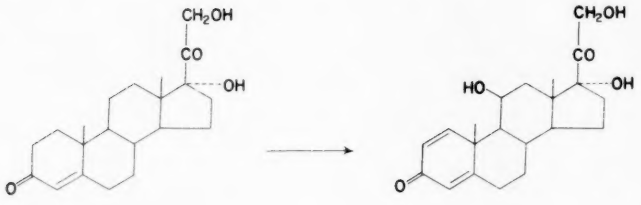
* With the co-operation of T. Kusunoki, K. Yoshino and H. Fujitani.

[1] H. Nawa, M. Uchibayashi, R. Takeda, I. Nakanishi, T. Kusaka, J. Terumichi, M. Uchida, M. Katsumata, K. Yoshino and H. Fujitani, Tetrahedron 4, 201 (1958).



Reichstein's Substance S (I) Prednisolone

Conditions for fermentation of Pseudomonas species 109, an organism identified as closely akin to Pseudomonas boreopolis,[1] were examined elaborately and as a result a trace of prednisolone together with II was detected as a transformation product of I on the paper chromatogram. The microorganism was then treated with ultra-violet ray (irradiation with a 30 W ultra-violet ray lamp at a distance of 54 cm for 1 - 5 min), and was incubated on a bouillon agar plate containing 0.1 per cent of I. Selection of the strain was conducted by paper-chromatographical examination of bioconversion products and a mutant could be isolated which showed an excellent ability of forming prednisolone.

The mutant of Pseudomonas sp. 109 thus obtained was incubated in a synthetic medium containing cornsteep-liquor, phosphates, sulphates, glycerol and urea, and fermentation of I was observed as described previously.[1] Extraction of the culture filtrate with ethyl acetate, followed by concentration of the extract afforded a crude steroid mixture which was

acetylated with acetic anhydride and pyridine and chromatographed on Florisil. Elution with a solvent pair of ether and acetone yielded the acetate of unchanged I and 21-acetoxy-1,4-pregnadiene-11β,17α-diol-3,20-dione (prednisolone acetate)[2] (m.p. 230°; υ^{Nujol} 3344, 3257, 1742, 1718, 1647, 1587, 1222 cm^{-1}; Found: C, 68.37; H, 7.38: Calc. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51), which was identified by comparison of paper chromatogram, melting point and infra-red spectrum with an authentic sample. The rate of transformation of the substrate I to prednisolone was 20 - 30 per cent.

The above finding clearly indicates that 1-dehydrogenation and 11β-hydroxylation were performed simultaneously be a single microorganism, and thus the one-step preparation of therapeutically valuable prednisolone from I was established for the first time. It is furthermore interesting to note that those enzymatic reactions can be conducted by microorganisms which belong to bacteria.

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[2] H. L. Herzog et al., Science 121, 176 (1955).

Tetrahedron Letters No.18, pp. 20-23, 1959. Pergamon Press Ltd. Printed in Great Britain.

TETRAHEDRAL "CYCLOBUTADIENE" ?

William N. Lipscomb

Harvard University, Chemistry Department, Cambridge 38, Massachusetts

(Received 4 November 1959)

RECENT experimental evidence[1] that C_4H_4 is stabilized in the ion $AgC_4H_4^+$ and that decomposition yields gas molecules which form $AgC_4H_4^+$ elsewhere from Ag^+ suggest reconsideration of the geometrical and valence structures of C_4H_4 itself. It is suggested here that a tetrahedral structure geometrically similar to that[2] of B_4Cl_4, might be stable.

The instability of planar cyclobutadiene has been discussed many times since it was first pointed out[3,4] that the simplest LCAO treatments lead to a triplet ground state showing orbital degeneracy, which, in non-linear molecules should lead to molecular rearrangement.[5,6] A more recent study[7] has shown that electron - electron interaction splits the $(a_{2u})^2(e_g)^2$ configuration into the four levels, $^1A_{1g}$, $^1B_{2g}$, $^3A_{2g}$ and $^1B_{1g}$, none of

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1 M. Avram, E. Marica and C. D. Nenitzescu, Chem. Ber. 92, 1088 (1959).

2 M. Atoji and W. N. Lipscomb, J. Chem. Phys. 21, 172 (1953); Acta Cryst. 6, 547 (1953).

3 E. Hückel, Grundzüge der Theorie ungesättigter und aromatischer Verbindungen, Verlag Chemie, Berlin (1938).

4 G. W. Wheland, Proc. Roy. Soc. A 164, 397 (1938).

5 H. A. Jahn and E. Teller, Proc. Roy. Soc. A 161, 220 (1937).

1959

which is orbitally degenerate. Hence, the Jahn - Teller theorm in its exact form does not apply; nevertheless, the presence of both filled and unfilled electronic levels at so nearly the same energy is extremely rare in polyatomic molecules containing an even number of electrons. Presumably such molecules, if not diatomic, are unstable with respect to distortions that yield filled levels which are more stable and unfilled levels which are less stable. A planar distortion would most likely lead to acetylene, whereas a non-planar distortion could lead to a tetrahedral structure.

In order to examine molecular orbitals in tetrahedral C_4H_4 the LCAO approximation already given[8] for B_4H_4 has been extended here to include resonance integrals ϵ between approximately tetrahedral orbitals on the same carbon atom, and resonance integrals η between orbitals non-coplanar with the C-C bond. The a_1 level lies at $H_o+\beta+2\gamma+4\delta+2\epsilon+2\eta$, the e pair of levels at $H_o+\beta-\gamma-2\delta-\epsilon+2\eta$, with a triply degenerate t levels between these.[8] Thus while B_4H_4 would have the configuration $(a_1)^2(t_1)^6$, C_4H_4 would have the configuration $(a_1)^2(t_1)^6(e)^4$. Reasons that the $(e)^4$ level is possibly slightly bonding include an argument based on approximate relative values of the integrals, and a comparison with the established structure of B_4Cl_4.

Assumption of reasonable hybrid orbitals in a range about that found[8] for cyclopropane yields values of overlap integrals corresponding to γ and δ about 1/3 of that corresponding to β. The term $\beta-\gamma-2\delta$ would, with the

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[6] H. A. Jahn, Proc. Roy. Soc. A 164, 117 (1938).

[7] W. Moffitt and J. Scanlan, Proc. Roy. Soc. A 220, 530 (1954).

[8] W. H. Eberhardt, B. L. Crawford, Jr. and W. N. Lipscomb, J. Chem. Phys. 22, 985 (1954).

hopeful assumption of proportionality to resonance integrals, lead to approximate non-bonding of these levels. Moreover, it is probable that η is negative, as are β, γ and δ, but comparison with the filled-orbital valence bond analogue[9] suggests that ϵ is positive essentially because of distortion of bonds from the tetrahedral configuration. Both of these additional interactions tend to stabilize further the highest filled e degenerate pair of levels in tetrahedral C_4H_4. It is more difficult to estimate either the strain energy or the nearly compensating additional resonance energy of various pairing schemes, but the additional interactions, particularly those between orbitals on the same carbon atom, may require even more bend in the equivalent bonds along tetrahedral edges than that found[8] in cyclopropane.

A stronger argument is that B_4Cl_4 exists, but that B_4H_4 has not yet been discovered. Although to a first approximation[8] the filled electron configuration is $(a_1)^2(t_1)^6$, it has been argued[10] that the interaction of the lone π pairs of Cl with the e levels is at least partly responsible for the existence of B_4Cl_4 as contrasted with B_4H_4. This interaction of levels with the same symmetry characteristics certainly suggests that the e pair of levels of the tetrahedral B_4 group cannot lie at a high energy, relative to the lone pairs of Cl, and probably that they lie at weakly bonding energy levels.

Whereas in B_4Cl_4 the e levels are filled by interaction with an electron donor, in tetrahedral C_4H_4 the e levels are already filled.

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[9] C. A. Coulson and W. Moffitt, Phil. Mag. 40, 1 (1949).

[10] H. C. Longuet-Higgins, Quart. Rev. 11, 121 (1957).

Hence it is suggested that stable molecules based upon a tetrahedral C_4 arrangement might be prepared if an electron acceptor, such as -COOH, $-BCl_2$, $-NO_2$ or -CN is substituted for -H in C_4H_4.

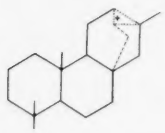
The geometry of the $AgC_4H_4^+$ complex depends upon whether one Ag^+ is bonded to C_4H_4, as it might be in solution, or whether each Ag^+ is bonded to two C_4H_4 and each C_4H_4 is bonded to two Ag^+ as may occur in the crystal. In either case, the symmetrical 5s orbital of Ag^+ would lie off the four-fold axis and off the molecular plane if C_4H_4 is planar or nearly so, or towards an opened edge, not a face, of the tetrahedron if the initially tetrahedral geometry is approximated.

In summary, it cannot be strongly argued that if C_4H_4 or one of its substitution derivatives exists, it must be tetrahedral, but this possibility of a closed shell electronic structure for this elusive molecule appears not to have been previously suggested.

E R R A T A

1. L. H. BRIGGS, B. F. CAIN, B. R. DAVIS and J. K. WILMHURST: The absolute configuration of phyllocladene, mirene, rimuene, cupressene and kaurene, Tetrahedron Letters No. 8, 13-16 (1959).

Formulae II and XIV on p. 14 of the above article were published with slight errors. The correct formulae appear below.



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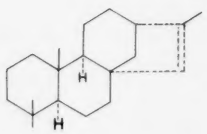

XIV

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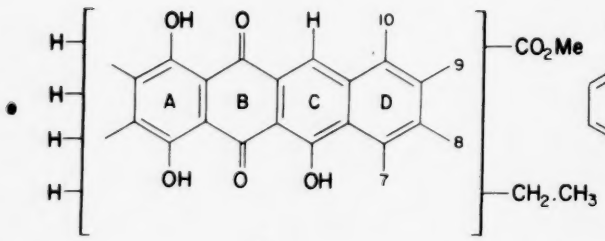
2. W. D. OLLIS, I. O. SUTHERLAND and J. J. GORDON: Rutilantinone, Tetrahedron Letters No. 16, 17-23 (1959).

An OH group was missing from formula II (Ring C) and from formula III (Ring A) in the above article. This has now been rectified and the corrected formulae are reproduced below.



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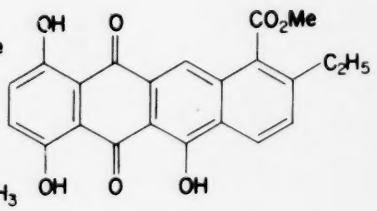

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1959

Tetrahedron Letters No.19, pp. 1-3, 1959. Pergamon Press Ltd. Printed in Great Britain.

NUCLEAR BROMINATION IN PHLOROGLUCINOL DERIVATIVES

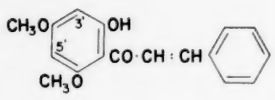
John A. Donnelly

Department of Chemistry, University College, Dublin

(Received 30 October 1959)

1959

SINCE Kostanecki and Tambor[1] reported nuclear substitution in the bromination of chalcones derived from phloroglucinol (e.g., I), workers[2,3,4] have assumed that it occurs in the 5'-position to form a tribromide which gives the 5-bromoaurone (II) with aqueous ethanolic potassium hydroxide.



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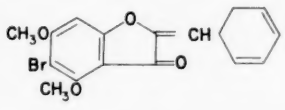

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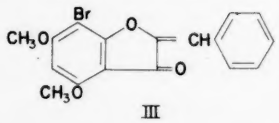

III

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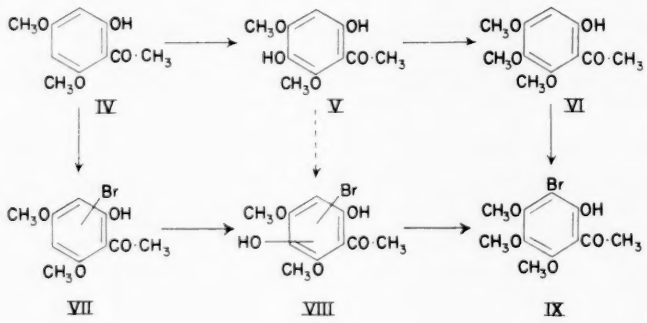
[1] St. v. Kostanecki and J. Tambor, Ber. 32, 2260 (1899).

[2] N. M. Cullinane and D. Philpott, J. Chem. Soc. 1761 (1929).

[3] D. R. Nadkarni and T. S. Wheeler, J. Univ. Bombay, 6, 107 (1937).

[4] W. A. Hutchins and T. S. Wheeler, J. Chem. Soc. 91 (1939).

It has now been found that the halogen atom enters in fact the 3'-position, so that the compounds previously formulated as in II are actually of type III. Wheeler (this department) has suggested that the resulting steric effects on the 2'-hydroxyl group facilitate the hitherto inexplicable formation of aurone rather than of the corresponding flavone from the so-called 5'-(actually 3'-)bromochalcones.



The monobrominated compound[5] (VII), obtained from 2-hydroxy-4,6-dimethoxyacetophenone (IV), gave VIII, m.p. 147-149° (ethanolic ferric colour - green), when treated with alkaline potassium persulphate. Compound VIII on further methylation yielded IX which was identical (mixed melting point) with authentic 3-bromo-2-hydroxy-4,5,6-trimethoxyacetophenone (IX), m.p. 89-90° (ethanolic ferric colour - green), prepared by

---

[5] A. R. Penfold, J. Proc. Roy. Soc. N.S.W. 61, 184 (1927).

brominating 2-hydroxy-4,5,6-trimethoxyacetophenone (VI).[6] Bromination of 2,5-dihydroxy-4,6-dimethoxyacetophenone (V),[6] for comparison with VIII, was unsuccessful.

3'-Bromo-2'-hydroxy-4',6'-dimethoxychalcone,[7] m.p. 185-187°, prepared from VII, and benzaldehyde was identical with the chalcone obtained by treating the tribrominated product of I with potassium iodide in acetone.

Satisfactory analyses were obtained for compounds VIII and IX.

The author wishes to thank Professor T. S. Wheeler for his interest and advice.

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[6] V. D. N. Sastri and T. R. Seshadri, Proc. Indian Acad. Sci. 23, 262 (1946).

[7] N. R. Bannerjee and T. R. Seshadri, Proc. Indian Acad. Sci. 36, 134 (1952).

1959

Tetrahedron Letters No. 19, pp.4-8, 1959. Pergamon Press Ltd. Printed in Great Britain.

A NEW METHOD FOR THE PREPARATION OF 4-HYDROXYFLAVANS

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H. Fletcher, E. M. Philbin and T. S. Wheeler

Department of Chemistry, University College, Dublin

(Received 30 October 1959)

FLAVANS containing a 4-hydroxyl group are of increasing importance because of a growing interest in flavan-3,4-diols (leucoanthocyanidins, I). Reduction of 4-oxoflavans (II), catalytically or otherwise, has been closely studied and much attention has been directed to the configuration and conformation of the 4-hydroxyl group produced.[1] An alternative approach now described, which contains features of stereochemical interest, involves reduction of a 4-oximinoflavan (III) to the amine (IV) which is then converted into a 4-hydroxyflavan (I).

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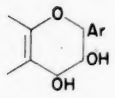
* Professor Bognar was Visiting Professor of Chemistry in University College, Dublin, for the Michaelmas term of 1958.

[1] See, for example, [a] R. Bognar and M. Rakosi, Chem. & Ind. 188 (1956); [b] Acta Chim. Acad. Sci. Hung. 13, 217 (1957); [c] Ibid. 14, 369 (1958); [d] K. Freudenberg and K. Weinges, Ann. 613, 61 (1958); [e] M. D. Kashikar and A. B. Kulkarni, Chem. & Ind. 1084 (1958). Further references are given in these citations.

1959

Previous workers regarded dihydroquercetin as inert to the usual ketonic reagents and attributed this inactivity to the effect of the adjacent hydroxyl group in the 3-position.[2] It has now been found, however, that hindrance by this group is not marked, for with aqueous pyridine as base, dihydroflavonol[3] gives an oxime, m.p. 153-154°, phenylhydrazone, m.p. 173-174°, and semicarbazone, m.p. 270° (decomp.), and 3-hydroxy-4'-methoxy-6-methylflavanone forms the oxime, m.p. 185-187°. Similar derivatives are obtained when the dihydroflavonol is substituted in the 5-position; for example dihydroquercetin phenylhydrazone, m.p. 218° (decomp.), and 3-hydroxy-5,7,3',4'-tetramethoxy-4-oximinoflavan, m.p. 194°.

The production of oximes suggested a route to the corresponding diols.



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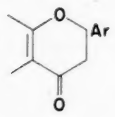

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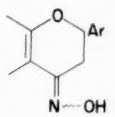

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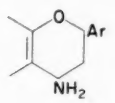

IV

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[2] H. L. Hergert, P. Coad and A. V. Logan, J. Org. Chem. 21, 304 (1956).

[3] This was prepared from the 2'-hydroxychalcone by oxidation by alkaline hydrogen peroxide (see L. Reichel and J. Steudel, Ann. 553, 83 (1942)). Treatment with sulphuric acid gave flavonol, an indication that the 3-hydroxyl group is equatorial (V. B. Mahesh and T. R. Seshadri, Proc. Indian Acad. Sci. 41, 210 (1955).

Hydrogenation of the oximes using PtO_2, Pd/C or $LiAlH_4$ gave the amines which were treated with nitrous acid. The successful experiments to date are outlined below. Some work on 4-oximinoflavan is included.

Flavan-3,4-diol. Reduction of 4-oximinodihydroflavonol catalytically (PtO_2) or with lithium aluminium hydride gave 4-amino-3-hydroxyflavan, m.p. 172-173°, which with nitrous acid yielded a new flavan-3,4-diol, m.p. 160° (dibenzoate, m.p. 118°). This diol formed an isopropylidene derivative, m.p. 110-111°, and, with phosgene, a carbonate, m.p. 159°.

4'-Methoxy-6-methylflavan-3,4-diol. 3-Hydroxy-4'-methoxy-6-methyl-4-oximinoflavan, gave 4-amino-3-hydroxy-4'-methoxy-6-methylflavan isolated as the acetate with m.p. 187-188°. The amine was converted into 3,4-dihydroxy-4'-methoxy-6-methylflavan, m.p. 193°, identical (mixed m.p. comparison) with the 2-p-C_6H_4OMe (e), 3-OH(e), 4-OH (e) diol obtained together with the 4-OH(a) isomer by Joshi and Kulkarni[4] from the corresponding dihydroflavonol and lithium aluminium hydride. The diol with m.p. 193° yielded an isopropylidene derivative, m.p. 126-127°. We are indebted to Dr. Kulkarni for a sample of his compound.

This identity with Joshi and Kulkarni's product suggests that flavan-3,4-diol (m.p. 160°) obtained from the amine as described above also has the larger groups - 2e,3e,4e. On the other hand Bognar and Rakosi,[1 a,c] isolated a diol, m.p. 145°, from dihydroflavonol using catalytic hydrogenation, $LiAlH_4$, or $NaBH_4$, and assigned to it the same conformation - 2e,3e,4e.

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[4] C. G. Joshi and A. B. Kulkarni, J. Indian Chem. Soc. 34, 753 (1957).

These results require further study since a trans-flavan-3e,4e,-diol would not be expected to yield a cyclic compound.[5] The formation of such derivatives merits consideration in the light of Philbin and Wheeler's[6] suggestion that five atoms of the dihydropyran ring in flavans are coplanar. Also recent investigations reduce confidence in the application of stereochemical rules.[1 a,7]

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α-4-Hydroxyflavan. 4-Oximinoflavan, m.p. 170-171°, on controlled catalytic reduction (Pd/C or PtO_2) formed 4-aminoflavan m.p. 112°, (acetate, m.p. 157-159°; hydrochloride, m.p. 268-273°); this with nitrous acid gave in good yield only α-4-hydroxyflavan, m.p. 118-119° (acetate, m.p. 85-87°).[8] The conversion with nitrous acid appears to be stereospecific.

Hydrogenation (Pd/C) of flavanone oxime until 3 moles of hydrogen had been absorbed yielded 1-amino-1-o-hydroxyphenyl-3-phenylpropane, m.p. 203-206°, identical (mixed m.p.) with an authentic specimen prepared by reduction of o-hydroxy-β-phenylpropiophenone oxime, m.p. 117-118°.[1 b,9] Many examples of such reductive decyclizations have been observed.[8 c,9]

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[5] D. H. R. Barton and R. C. Cookson, Quart. Rev. 10, 82 (1956).

[6] E. M. Philbin and T. S. Wheeler, Proc. Chem. Soc. 167 (1958); cf. H. Hart and C. R. Wagner, Ibid. 284 (1958).

[7] W. Huckel, M. Maier, E. Jordan and W. Seeger, Ann. 616, 46 (1958), K. D. Hardy and R. J. Wicker, J. Amer. Chem. Soc. 80, 640 (1958).

[8] For previous work on α- and β-4-hydroxyflavans see: [a] K. Freudenberg and L. Orthner, Ber. 55, 1748 (1922); [b] P. Karrer, Y. Yen and I. Reichstein, Helv. Chim. Acta 13, 1308 (1930); [c] R. Mozingo and H. Adkins, J. Amer. Chem. Soc. 60, 669 (1938); [d] T. A. Geissman and R. O. Clinton, J. Amer. Chem. Soc. 68, 700 (1946); [e] V. N. Gupta, A. C. Jain and T. R. Seshadri, Proc. Indian Acad. Sci. 38, 470 (1953); [f] J. E. Gowan, S. P. MacGiolla Riogh, G. J. MacMahon, S. O'Cleirigh, E. M. Philbin and T. S. Wheeler, Tetrahedron 2, 116 (1958).

[9] T. Tasaki, Acta Phytochim. 3, 259 (1927); Chem. Abstr. 23, 125 (1929).

Satisfactory analyses have been obtained for new compounds.

Work is in hand on the use of 3-aminoflavanones (from 3-isonitrosoflavanones) for the synthesis of derivatives of flavan-3-ol.[10]

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[10] Immediately before this paper was submitted for publication information was received that similar work on 3-aminoflavanones was independently in progress in the Institute of Science, Bombay, under the direction of Dr. A. B. Kulkarni.

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A NEW METHOD FOR THE PREPARATION OF NAPHTAZARINS

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(Received 2 November 1959)

AMONG quinone pigments, the derivatives of naphtazarin (5,8-dihydroxy-1,4-naphtoquinone) present a special interest, not only because they are important natural products, the structure of which has not been elucidated in many cases, but also because they have been employed as colouring matter for industrial application.

The methods of synthesis of naphtazarin derivatives are not, however, very satisfactory. Roussin[1] obtained naphtazarin for the first time by the action of fuming sulphuric acid and a reducing agent on the 1,5-dinitronaphtalene, but the method was not applied to the homologues until Bruce and Thomson,[2] who obtained in low yield 2-methylnaphtazarin, 2,6-dimethylnaphtazarin and 2,6-dichloronaphtazarin starting with the

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[1] Z. Roussin, C. R. Acad. Sci., Paris 52, 1033 (1861).

[2] D. B. Bruce and R. H. Thomson, J. Chem. Soc. 1089 (1955).

appropriate dinitronaphtalenes. Zahn and Ochwat[3] developed a method of synthesis of naphtazarins by condensing hydroquinones with maleic anhydride, or derivatives, in fused sodium chloride-zinc or aluminium chloride. This method has been applied, for example, to the preparation of hydroxydroserone[4] from maleic anhydride and 2-methyl-3-methoxyhydroquinone and of echinochrome A[5] using 2-ethyl-1,3,4-trimethoxybenzene and dibenzoyloxymaleic anhydride, although in this case the yield is only 1.5 - 2 per cent.

In our study on diene synthesis with quinones, we experimented with the preparation of naphtazarins from the adducts of butadiene, or derivatives, with p-benzoquinones, which are usually obtained readily and in good yields. We tried in this way to develop a more satisfactory method of synthesis of the natural products in question, especially the spinochromes and echinochromes.

The butadiene-p-benzoquinone adduct (I) by acetylation with acetic anhydride was transformed in the acetate of the diphenolic form (II). The oxidation in α of this product could lead to the naphtazarin diacetate (III). However, if it is carried out with selenium dioxide only the aromatized product, the naphtohydroquinone diacetate (IV), is obtained, while by oxidation with chromic anhydride at 0°C the naphtazarin diacetate (III) is formed, and this by alkaline hydrolysis yields naphtazarin (V).

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[3] K. Zahn and P. Ochwat, Ann. 462, 72 (1928).

[4] A. K. Macbeth, J. R. Price and F. L. Winzor, J. Chem. Soc. 334 (1935).

[5] K. Wallenfels and A. Gauhe, Ber. 76, 325 (1943).

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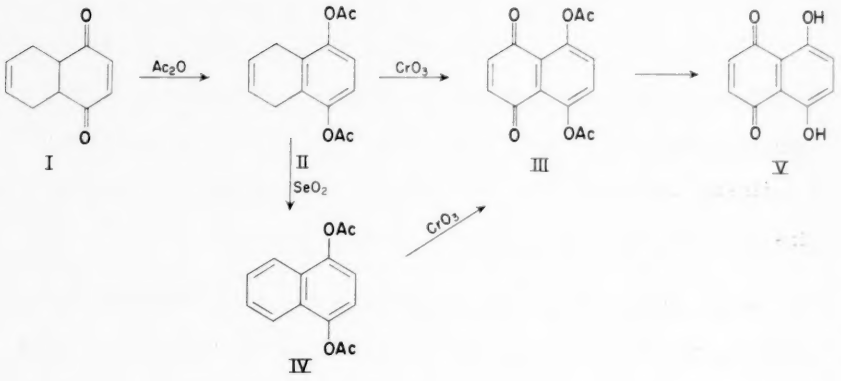

On the other hand, the chromic oxidation of the naphtohydroquinone diacetate (IV) leads, in the same experimental conditions, to the naphtazarin diacetate (III). It is possible, therefore, that the chromic oxidation of the acetylated adduct takes place first with aromatization of the naphtohydroquinone diacetate, which on oxidation gives the diacetyl derivative of naphtazarin.

Because of the tautomeric character of the naphtazarin, it is known that the same compound is obtained by condensing either maleic anhydride with toluhydroquinone or citraconic anhydride with hydroquinone.[6] In our

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[6] A. K. Macbeth, J. R. Price and F. L. Winzor, J. Chem. Soc. 333 (1935).

case the same methylnaphtazarin is obtained from the butadiene-toluquinone or 2-metilbutadiene-p-benzoquinone adduct. This allows the use of the dienes or quinones most suitable in each case.

The new process seems to be of general application and the preparation of several substituted naphtazarins from the corresponding Diels - Alder adducts (butadiene-quinone; butadiene-toluquinone; isoprene-quinone; 2,3-dimethylbutadiene-quinone; 2,3-dimethylbutadiene-toluquinone; 2,3-dimethylbutadiene-methoxyquinone) has been studied.

In all cases the acetyl derivative of the adduct has been obtained by refluxing with acetic anhydride for 2 or 3 hr. As an example of the experimental conditions the details for the last steps of the obtention of methylnaphtazarin are given below:

To 36 g of chromic anhydride dissolved in the smallest possible quantity of 80 per cent aqueous acetic acid, a solution of 24 g of 1,4-dihydroxy-5,8-dihydro-7-methylnaphtalene diacetate (from the isoprene-p-benzoquinone adduct) in glacial acetic acid is added, drop by drop and with constant stirring, keeping the temperature under 5°C. The stirring is continued for several hours and the greenish solution formed is poured over 500 ml of ice water. The yellow precipitate of methylnaphtazarin diacetate formed is filtered, washed with water and recrystallized from alcohol, m.p. 169,5° C. Yield 75 per cent.

The methylnaphtazarin diacetate is hydrolysed by heating in a water bath with 5 per cent aqueous sodium hydroxide. The solution of an intense blue colour is filtered and acidified with hydrochloric acid, the red precipitate of methylnaphtazarin being collected. Red-brown needles are

obtained by sublimation. Recrystallization from alcohol gives needles, m.p. 175° C.

Studies are in progress on the preparation of oxyderivatives of the type of echinochromes and spinochromes and of higher condensed systems from adducts with naphtoquinone.

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CIS OXYMERCURATION OF NORBORNENE

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(Received 3 September 1959; in revised form 9 November 1959)

TWO different mechanisms for oxymercuration, one involving cis addition[2] and another involving trans addition[3], have been previously proposed. Recent deoxymercuration studies[4-5], have shown that olefins add mercuric salts in a trans fashion just as do simple acetylenes. This communication reports the first case of cis oxymercuration of an olefin (norbornene) and an ionic addition to norbornene which is not accompanied by rearrangement.

The intermediate (I) has been written[6] to explain the products of ionic additions to the double bond in the 2,2,1-bicycloheptene series.

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[1] This work was carried out at The Dow Chemical Company, Pittsburg, California.

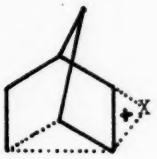
[2] O. W. Berg, W. P. Lay, A. Rodgman, and G. F Wright, Can. J. Chem. 36, 358 (1958) and other references found therein.

[3] H. J. Lucas, F. R. Hepner, and S. Winstein, J. Am. Chem. Soc. 61, 3102 (1939).

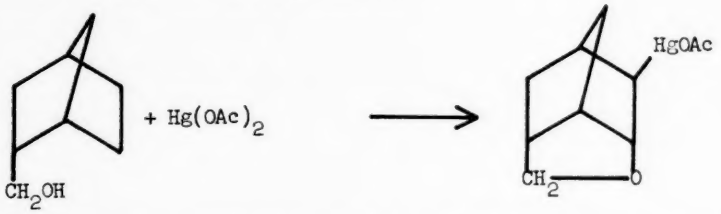
[4] M. M. Kreevoy, Abstracts 135th Meeting of The American Chemical Society, Boston, Massachusetts, April, 1959, page 81-O.

[5] T. G. Traylor and S. Winstein, ibid., page 82-O.

[6] H. Kwart, et al., J. Am. Chem. Soc. 76, 4072, 5400 (1954); 78, 5678 (1956).



Inversion at C_3 or C_4 would lead to the 2,3-trans and 2,7-syn products which are usually obtained[7-8]. Addition of iodine[9], acid[10], or mercuric acetate[10] to endo-2-hydroxymethyl-5-norbornene yields cyclic ethers indicating that oxygen competes successfully with C_5 in the opening of the olefin-X^+ complex (e. g., Equation 1).



(1)

However, in the addition of mercuric salts to unsubstituted norbornene an entirely different situation obtains. Neither trans addition nor rearrangement occurs; the only product being the exo-cis oxymercurial.

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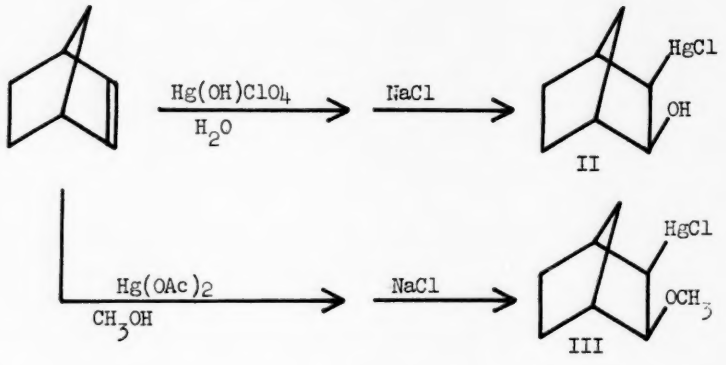
[7] W. G. Woods, R. A. Carboni, and J. D. Roberts, ibid., 78, 5653 (1956).

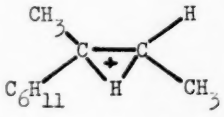
[8] H. M. Walborsky and D. F. Loncrini, ibid., 76, 5397 (1954).

[9] Interchemical Corporation, Commercial Development Department Bulletin CD-104.

[10] H. B. Henbest and B. Nichols, J. Chem. Soc. 1959, 221.



The cis opening of the intermediate (I) is as novel in general oxymercuration reactions as it is in ionic additions to norbornene and bears a striking resemblance to the cis opening of the substituted ethylene protonium ion IV reported recently by Cram and Tadanier[11].



IV

These observations suggest that mercury and hydrogen are much more strongly solvated than are other positive ions in this type of intermediate. However, the cis opening of the ion (I) is quite exceptional in mercuration reactions and recommends the exercise of caution in generalizing cis openings of such cyclic intermediates.

The oxymercurial (II), obtained in 86% yield by treating norbornene

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[11] D. J. Cram and J. Tadanier, J. Am. Chem. Soc. 81; 2745 (1959).

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with aqueous mercuric hydroxyperchlorate (followed by precipitation as the chloride), analyzed accurately for $C_7H_{11}HgClO$, and had a single hydroxyl stretching frequency at 3604.0 cm.$^{-1}$ in carbon tetrachloride. It could be oxidized in 73% yield with alkaline permanganate to a ketone C_7H_9HgClO (1724.1 cm.$^{-1}$) in which the mercury was adjacent to the keto group. This was evidenced by its facile removal with stannite or iodide ions[12] to produce norcamphor.

The oxymercurial (II) was reduced with sodium amalgam to exo-norborneol which was then converted to the acetate. The infrared spectrum of this acetate was identical to that of exo-norbornyl acetate reported by Winstein and Trifan.[13]

The relative configurations of the mercury and methoxy groups in the 3-methoxy-2-norcamphanylmercuric chloride (III) can be established with the data of Wright et al.[14] In general, the dipole moments of oxymercuration products have been found to be higher than those of their diasteriomers which are obtained by carbon-mercury epimerization.[14] This is true of cyclopentene and cyclohexene oxymercuration products. However, III was found to have a dipole moment of 4.22 D whereas its diasteriomer had a dipole moment of 2.77 D. Because the cyclopentene and cyclohexene oxy-

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[12] O. A. Reutov and Lu Tszin Chzhu, Doklady Akad. Nauk. S. S. S. R. 110, 575-7 (1956).

[13] S. Winstein and D. Trifan, J. Am. Chem. Soc. 74, 1148 (1952).

[14] M. J. Abercrombie, A. Rodgman, K. R. Bharucha, and G. F Wright, Can. J. Chem. 37, 1328 (1959).

mercuration products have been shown to be trans,[4] the norbornene adduct must be exo-3-methoxy-exo-2-norcamphanylmercuric chloride (III).[15]

The authors wish to thank Dr. M. M. Kreevoy for helpful discussions.

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[15] After this work was completed, there appeared a publication[14] reporting an identical oxymercuration of norbornene. This paper purports to prove that the adduct (II) is endo-3-hydroxy-exo-2-norcamphanylmercuric chloride by its reduction to "endo-norborneol". We have repeated the reduction procedure outlined, to obtain their "endo-norborneol" which has proven to be di-(exo-3-hydroxy-2-norcamphanyl) mercury (by infrared and C, H, Hg analyses). There was also produced, in 35% yield, exo-norborneol which apparently escaped the observation of these workers. In addition, reduction of 3-methoxy-2-norcamphanylmercuric chloride with sodium stannite yields, not endo-norbornyl methyl ether as reported, but exo-norbornyl methyl ether identified by comparing its infrared spectrum with that of the ether obtained by adding methanol to norbornene in sulfuric acid. Therefore, their configurational assignments and mechanistic interpretations based on these assignments[16] are incorrect.

[16] D. D. K. Chiu and G. F Wright, Can. J. Chem. 37, 1425 (1959).

Tetrahedron Letters No. 19, pp. 19-28, 1959. Pergamon Press Ltd. Printed in Great Britain.

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THE BIOSYNTHESIS OF DERIVATIVES OF ALLYLIC ALCOHOLS FROM [2-^{14}C] MEVALONATE IN LIVER ENZYME PREPARATIONS AND THEIR RELATION TO SYNTHESIS OF SQUALENE

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STUDIES on the enzymic synthesis of squalene from mevalonic acid (3:5-dihydroxy-3-methylpentanoic acid) in yeast extracts have revealed a number of new intermediates. 5-Phosphomevalonate,[1,2,3] 5-diphosphomevalonate and 3-methylbut-3-en-1-yl pyrophosphate (isopentenyl pyrophosphate)[4,5,6] have been recognized as successive intermediates in the synthesis of squalene. In addition, Lynen et al.[5] found that a protein fraction of yeast extracts catalysed the synthesis from mevalonate of farnesyl pyrophosphate which was

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1 T. T. Tchen, J. Amer. Chem. Soc. 79, (1957).

2 T. T. Tchen, J. Biol. Chem. 233, 1100 (1958).

3 F. Lynen, Ciba Symposium on Biosynthesis of Terpenes and Sterols p. 95. J. & A. Churchill, London (1959).

4 S. Chaykin, J. Law, A. H. Phillips, T. T. Tchen and K. Bloch, Proc. Nat. Acad. Sci. Wash. 44, 998 (1958).

5 F. Lynen, H. Eggerer, U. Henning and I. Kessel, Angew. Chem. 70, 739 (1958).

6 U. Henning, E. M. Möslein and F. Lynen, Arch. Biochem. Biophys. 83, 259 (1959).

converted to squalene on addition to yeast cell particles and reduced pyridine nucleotides.

Experiments on the same problem with liver enzymes indicate that the reactions of squalene biosynthesis in mammalian cells are similar to those occurring in yeast cells. 5-Phosphomevalonate and 5-diphosphomevalonate and the enzymes responsible for their formation in liver extracts have already been described.[7-11] I wish to report briefly the synthesis by liver enzymes of derivatives of allylic alcohols ("polyprenols"), which have properties similar to those described by Lynen et al.[5] for farnesyl pyrophosphate.

Two types of enzyme preparations were used. One was a protein fraction (F_{30}^{60}-enzymes), precipitable between 30 and 60 per cent ammonium sulphate saturation, of the supernatant of rat liver homogenates[12] centrifuged at 105,000 *g* for 60 min. This precipitate was dissolved in 0.02 M $KHCO_3$ and dialysed against the same for 3 - 4 hr. to give a protein content of 30 - 50 mg/ml. The second preparation was a suspension of liver-cell microsomes isolated from the homogenates.[13]

When the F_{30}^{60}-enzymes were incubated with DL-[2-^{14}C]mevalonate,

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[7] A. de Waard, Doctoral Thesis: Investigations on the Intermediates in the Biosynthesis of Fatty Acids and Cholesterol, University of Utrecht. Drukkerij Gebr. Janssen, Nijmegen (1958).

[8] G. Popják, Ciba Symposium on Biosynthesis of Terpenes and Sterols p. 148. J. & A. Churchill, London (1959).

[9] A. de Waard and G. Popják, Biochem. J. 73, 410 (1959).

[10] H. R. Levy and G. Popják, Biochem. J. 72, 35P, (1959).

[11] H. R. Levy and G. Popják, Biochem. J. Submitted for publication.

[12] N. L. R. Bucher and K. McGarrahan, J. Biol. Chem. 222, 1 (1956).

[13] G. Popják, L. Gosselin, I. Y. Gore and R. G. Gould, Biochem. J. 69, 238 (1958).

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adenosinetriphosphate (ATP) and Mg^{2+} ions aerobically or anaerobically, in the presence of absence of reduced pyridine nucleotides, only traces of radioactivity could be extracted with light petroleum (b.p. 40 - 60°) from the alkaline incubation mixture after saponification with 2 N KOH. On the other hand when the alkaline digests were made acid (pH about 2) with H_2SO_4, ^{14}C-labelled substances could be readily extracted with light petroleum. Although such substances might be thought to be acidic in character, partitioning between aqueous alkali (0.2 N KOH or $KHCO_3$) and light petroleum showed that only 10 - 15 per cent of these was acidic and the larger fraction 85 - 90 per cent, neutral in character. The results of a typical experiment are shown in Table 1, which also demonstrate that both ATP and Mg^{2+} ions are needed for the formation of these substances.

Both the neutral and acidic products (the latter after methylation with diazomethane) were analysed by gas-liquid radiochromatography (GLRC).[14] The neutral products contained several components, which had retention volumes identical with a number of branched chain primary and tertiary alcohols on columns with both polar (ethyleneglycol - adipate polyester) and non-polar (Apiezon-L) stationary phases at 197°C. The following substances were found: dimethylallyl alcohol, linalool, nerol (cis-geraniol), geraniol, nerolidol, trans - trans-farnesol and two further substances with retention volumes expected of the C_{20} analogues of nerolidol (geranyllinalool) and of farnesol (geranylgeraniol). In the specimen of neutral products, pooled from incubation nos. 1, 4, 5 and 6 of the experiment shown in Table 1, 62 per cent of the ^{14}C was present in nerolidol, 19.50 per cent in farnesol

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[14] G. Popják, A. E. Lowe, D. Moore, L. Brown and F. A. Smith, J. Lipid Res. 1, In Press (1959).

TABLE 1. SYNTHESIS OF NEUTRAL AND ACIDIC SUBSTANCES FROM DL-[2-^{14}C] MEVALONATE WITH SOLUBLE ENZYME FRACTION (F_{30}^{60}) OF RAT LIVER

The complete system contained in a final volume of 4 ml: 97.5 mg F_{30}^{60}-protein; 30 μmoles of ATP; 20 μmoles of $MgCl_2$; 400 μmoles of potassium hydrogen phosphate buffer, pH 7.5; 40 μmoles of NaF; 5 μmoles of DL-[2-^{14}C]mevalonate (140,000 counts/min at negligible thickness). Omissions from and additions to this system were made as shown.

Incubation no.	Enzyme system, omissions and additions	^{14}C counts found	
		In neutral products	In acidic products
1.	Complete	30,220	4122
2.	No Mg^{2+}	19	0
3.	No ATP; +ADP (30 μmoles)	2400	214
4.	+TPNH (2 μmoles)	27,690	4018
5.	+TPN (2 μmoles)	25,130	3966
6.	+TPNH + DPNH (2 μmoles each)	25,170	2370

and the remainder nearly equally distributed among the other components mentioned.

It follows from the mode of isolation of these alcohols that they did not occur in the free form, but were derivatives of some kind resistant to alkali but unstable in the presence of acid. Lynen et al.[5] noted that farnesyl pyrophosphate, isolated from incubations of yeast extracts with mevalonate, split into inorganic pyrophosphate and an organic residue on addition of 5 per cent trichloroacetic acid. It seems highly probable that the alcohols in the liver enzyme incubations were also present as the

pyrophosphates.

The unhydrolysed derivatives of the polyprenols could be extracted quantitatively from the slightly alkaline (pH 7.5) enzyme incubation mixtures with collidine as was also found for farnesyl pyrophosphate.[5] An aqueous solution of these derivatives could be prepared by shaking the collidine extract with aqueous 0.01 M $KHCO_3$ and ether, the polyprenol derivatives being transferred into the aqueous phase. When a sample of such an aqueous solution (aq.-PP) was acidified to pH 2 the free alcohols could be readily extracted with light petroleum. GLRC revealed the same substances and in the same ratios as were noted when the alcohols were extracted directly from the acidified enzyme incubations.

In view of the instability of esters of allylic alcohols in the presence of acid, one must beware of a rearrangement to a tertiary alcohol during elimination, induced by acid, from the ester of a primary allylic alcohol. Thus farnesyl pyrophosphate may yield not only farnesol but also nerolidol, and geranyl pyrophosphate may give rise to geraniol and to linalool. Elimination from an ester of an allylic alcohol in the presence of acid may occur readily, for the resulting electron deficient species may be partially stabilized by resonance between two mesomeric forms (a) $>C = \underset{|}{C} - \overset{+}{C}<$ and (b) $>\overset{+}{C} - \underset{|}{C} = C<$, which in the presence of water may yield either the primary or the tertiary alcohol.

It was particularly important to know whether the nerolidol found was genuinely an enzymic product, or merely resulted from the rearrangement of an ester of farnesol. A sample of aq.-PP (pH 8.5) after extraction with light petroleum was hydrolysed with snake venom (Naja flava) phosphatases at pH 8.3 in 0.15 M trishydroxymethyl-aminomethane buffer at 37° for 2,

24 and 48 hr. The alkaline incubation mixture was then extracted with light petroleum; analysis of the extracts by GLRC showed only the presence of dimethyl allyl alcohol, geraniol, nerolidol and of farnesol. However, whereas after acidification the amount of nerolidol was usually three times greater than that of farnesol, after the snake venom hydrolysis the amount of farnesol was four to six times greater than that of nerolidol. One further test, suggested by Dr. J. W. Cornforth, was carried out to ascertain whether or not the nerolidol was a genuine enzymic product. A freeze-dried sample of aq.-PP was reduced with $LiAlH_4$ in dry ether as used by Karrer and Jucker[15] for the fission of cetylphosphate. Approximately one-half of the polyprenols, originally bound in the specimen, appeared in the neutral fraction after reduction; these - according to GLRC analysis - consisted of two hitherto unidentified components (?hydrocarbons) and of nerolidol and farnesol; the ratio of the amounts of the latter two being 1:5.

These two tests leave little doubt of the genuine enzymic formation of a nerolidyl ester, most probably the pyrophosphate. The preponderence of nerolidol, and the finding or nerol and linalool in the specimens after release of the polyprenols from their conjugates by acid is no doubt due to the rearrangement discussed earlier. The most probable mechanism of the formation of nerolidyl pyrophosphate is the isomerization of farnesyl pyrophosphate by an intramolecular rearrangement:

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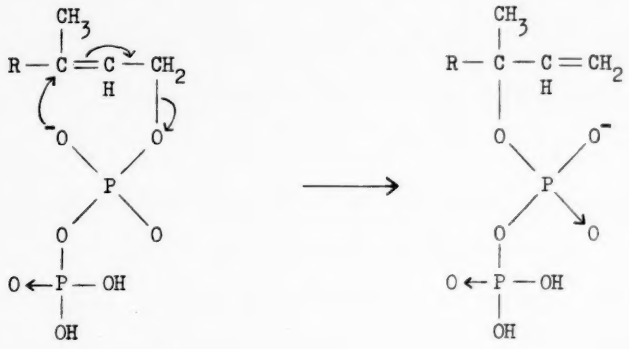
[15] P. Karrer and E. Jucker, Helv. Chim. Acta 35, 1586 (1952).



Further experiments indicated that the polyprenol derivatives are intermediates in the biosynthesis of squalene (and hence of cholesterol), the immediate precursors being, most likely, the farnesyl and nerolidyl esters.

In an experiment, the results of which are shown in Table 2, F_{30}^{60}-enzymes were first incubated on a large scale for 2 hr with DL-[2-^{14}C]mevalonate, ATP and Mg^{2+} ions. During this time about 25 per cent of the DL-mevalonate added was converted into the polyprenol derivatives, a small amount of acidic products being also formed. Several 4 ml samples of this preliminary bulk incubation were then treated in different ways. As is shown in Table 2, the addition of microsomes (0.2 ml suspension), ascorbic acid (30 μmoles) and of TPNH + DPNH (2 μmoles each), followed by incubation for a further 1 hr with air as gas phase, resulted in the formation of squalene, of cholesterol, and of carboxylic acids at the expense of the polyprenols. Analysis by GLRC showed that the farnesol and nerolidol components of the polyprenol mixture were principally involved in the change. In incubation no. 1, Table 2, 25,560 counts out of the 40,980

found in polyprenols were in farnesol + nerolidol; after addition of microsomes, ascorbate and of TPNH + DPNH this was reduced to 8355, a loss of 17,205 counts, of which 16,200 could be accounted for by the squalene and cholesterol synthesized.

In the absence of either ascorbate, or of TPNH + DPNH very little squalene and sterol was formed but the polyprenols were converted into carboxylic acids. The results of Table 2 show further (incubations nos. 3, 4 and 5) that when squalene was not synthesized on account of the omission of one or more essential coenzyme, there was a net loss of ^{14}C from the incubations. This suggests a catabolic disposal of squalene precursors by a mechanism as yet undetermined.

That the carboxylic acids are not intermediates in squalene biosynthesis was indicated by the fact that when these were allowed to accumulate in an incubation the subsequent addition of ascorbate and pyridine nucleotides failed to cause the synthesis of squalene and cholesterol (cf. incubation nos. 5 and 6, Table 2). These carboxylic acids appear to inhibit the utilization of the polyprenol derivatives for the synthesis of squalene.

Analysis of the methyl esters of the acids by GLRC revealed the same components as were noted previously[16] in incubations of whole homogenates and in the unfractionated supernatants of these obtained by centrifugation at 105,000 g. These were: trans-geranate, trans - trans-farnesoate (trans - trans-3:7:11-trimethyldodeca-2:6:10-trienoate) and the C_{20} all-trans 3:7:11:15-tetramethylhexadeca-2:6:10:14-tetraenoate. In

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[16] G. Popjak, M. Horning, N. L. R. Bucher and R. H. Cornforth, Biochem. J. 72, 34P (1959).

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TABLE 2. UTILIZATION OF POLYPRENOL DERIVATIVES FOR SQUALENE AND STEROL SYNTHESIS AND THEIR CONVERSION INTO TERPENOID ACIDS BY MICROSOMES

First F_{30}^{60}-enzymes were incubated for 2 hr at 37° with ATP and Mg^{2+} ions in a total volume of 60 ml. Each 4 ml of this bulk incubation contained 80 mg of proteins, and the same reagents as shown in Table 1 + 120 μmoles of nicotinamide. At the end of 2 hr 4 ml samples were withdrawn for analysis of products (incubation no. 1) and for setting up of further incubations for another 1 hr with microsomes as described in the text. All data below relate to a volume of 4 ml of the original bulk incubation.

Incubation no.	Additions after preliminary incubation	^{14}C counts found in products			
		Polyprenols	Squalene +sterol	Acids	Total
1.	None; F_{30}^{60}-enzymes alone	40,980	0	990	41,970
2.	Microsomes + ascorbate + DPNH + TPNH	15,150	16,200	13,030	44,380
3.	Microsomes + ascorbate	13,370	750	18,770	32,890
4.	Microsomes + DPNH + TPNH	12,410	2950	8700	24,060
5.	Microsomes	17,280	460	10,160	27,900
6.	Microsomes, and after 3rd hr +ascorbate + DPNH + TPNH	9400	1026	14,170	23,576

addition to these three acids, several others - in smaller amounts - were also found but not identified. Acids are formed only in small amounts by the F_{30}^{60}-enzymes alone, but their yield increases substantially in the presence of microsomes. In the previous communication[16] about the synthesis of terpenoid acids in liver enzyme preparations it was said that

the yields of the acids in the F_{30}^{60}-preparations was as good as in the whole homogenates or in their unfractionated supernatants. This was a mis-statement made in good faith, for it was not appreciated at that time that most of the petroleum-soluble substances released after acidification of the saponified F_{30}^{60}-incubations were neutral in character. In whole homogenates and in unfractionated supernatants of these only small amounts of the polyprenols can be found after 2 - 3 hr of incubation with mevalonate, the acidic products predominating (disregarding squalene and cholesterol synthesized in the whole homogenates).

Identification of the polyprenols, like that of the acids, synthesized from [2-^{14}C] mevalonate in liver enzyme incubations rests at present entirely on the GLRC analysis in which the ^{14}C-labelled substances had retention volumes indistinguishable from those of authentic marker substances, which were cochromatographed with the biosynthetic specimens. The power of resolution of these columns, however, was such that trans - trans (or trans) isomers were well separated from cis - trans (or cis) isomers.

The theoretical implications of the results described are discussed in the accompanying communication.[17]

I am indebted to Dr. M. Stoll of Firmenich et Cie, Geneva, for specimens of farnesol and nerolidol, to Dr. B. C. L. Weeden of the Imperial College of Science and Technology, London, for samples of geraniol, nerol, methyl-trans-geranate and methyl-cis-geranate, to Dr. Rita H. Cornforth of the National Institute for Medical Research, London, for farnesoic acid, and to Dr. Karl Folkers of Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, U. S. A., for a specimen containing the isomers of 3:7:11:15-tetramethylhexadeca-tetraenoic acid.

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[17] J. W. Cornforth and G. Popják, Tetrahedron Letters No. 19 29 (1959).

Tetrahedron Letters No. 19, pp. 29-35, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

MECHANISM OF BIOSYNTHESIS OF SQUALENE FROM SESQUITERPENOIDS

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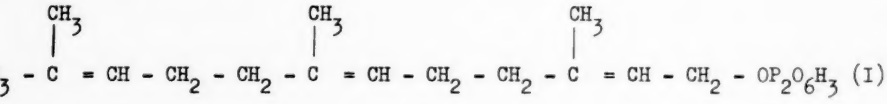
Medical Research Council, Experimental Radiopathology Research Unit,

Hammersmith Hospital, London

(Received 9 November 1959)

ALTHOUGH farnesyl pyrophosphate (I) has been shown to produce squalene when incubated with yeast cell particles and reduced triphosphopyridine nucleotide,[1] the detailed mechanism of this change is still unknown. The two hypotheses previously advanced[1,2] are incompatible with the new data[2] obtained by using hydrogen isotopes to study the biosynthesis of squalene from mevalonic acid.



We now propose an alternative scheme based on the discovery of acid-labile derivatives, presumably pyrophosphates, of both nerolidol and farnesol in a liver enzyme system after incubation with mevalonate.[3]

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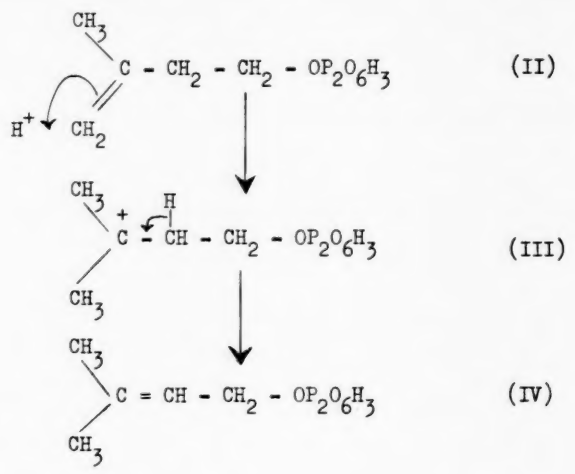
[1] F. Lynen, H. Eggerer, U. Henning and I. Kessel, Angew. Chem. 70, 739 (1958).

[2] H. C. Rilling and K. Bloch, J. Biol. Chem. 234, 1424 (1959).

The association of C_5 units, derived from mevalonate, to polyisoprenoid structures is thought to begin with the enzymic isomerixation[4] of isopentenyl pyrophosphate (II) to 3:3-dimethylallyl pyrophosphate (IV).



This process can be formulated chemically as the electrophilic addition of a proton to the reactive terminal double bond in (II). The resulting cation (III) then stabilizes itself by expulsion of a different proton to give (IV). Variants of this basic mechanism can be written: for example, fusion of the two steps into a concerted electron-shift, or (as Lynen suggested[4]) an intermediate neutralization of the cation (III) by attachment of a sulphydryl anion.

3:3-Dimethylallyl pyrophosphate, in common with other substances in which a potentially anionic group is in the α-position to a double bond, can

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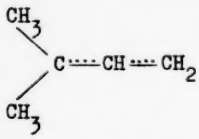
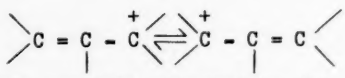
[3] G. Popjak, Tetrahedron Letters No. 19, 19 (1959).

[4] B. W. Agranoff, H. Eggerer, U. Henning and F. Lynen, J. Amer. Chem. Soc. 81, 1254 (1959).

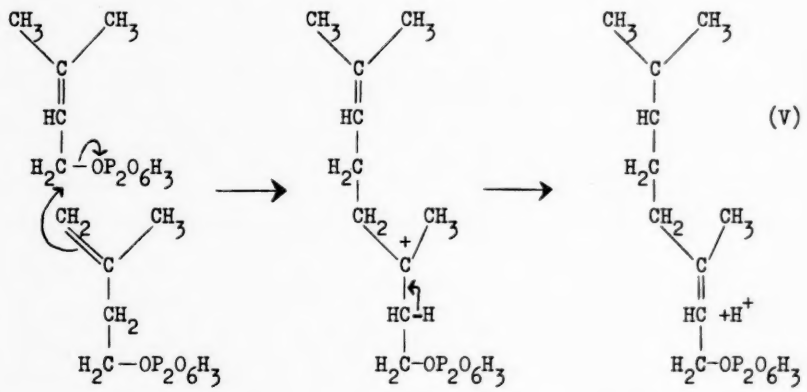
be expected to lose the pyrophosphate ion rather readily. The resulting electron deficient species,



, is partially stabilized by mesomerism between two equivalent forms (

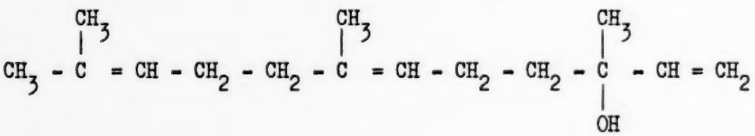


). A molecule of isopentenyl pyrophosphate could be attacked by this cation as already described for attack by a proton. The product is geranyl pyrophosphate (V), itself an allylic derivative which by loss of pyrophosphate and attack on a third molecule of isopentenyl pyrophosphate can produce farnesyl pyrophosphate (I). In these condensations variants in the timing of the electron-shifts can again be formulated; the mechanism as set forth is, however, essentially similar to that postulated by Lynen[1] and by Bloch.[2]



(V)

The presence in liver-enzyme system, after incubation with mevalonate, of a hydrophilic acid-labile derivative of nerolidol (VI), can readily be



(VI)

explained as arising from farnesyl pyrophosphate by anionotropy to give the derivative $R-\overset{\overset{CH_3}{|}}{\underset{\underset{X}{|}}{C}}\ CH=CH_2$ (cf. also ref.[3]) The group X is presumably, but for the present argument not necessarily, pyrophosphate.

R - C(CH3) = CH - CH2 - OP2O6H3 (I)
CH2 = CH - C(X)(CH3) - R (VII)
R - C(CH3) = CH - CH2 - CH(H) - CH+ - C(X)(CH3) - R (VIII)
R - C(CH3) = CH - CH2 - CH = CH - C(X)(CH3) - R
R - C(CH3) = CH - CH(H) - CH+ - CH = C(CH3) - R
R - C(CH3) = CH - CH = CH - CH = C(CH3) - R (IX)
TPNH + H+
R - C(CH3) = CH - CH2 - CH2 - CH = C(CH3) - R (X)

In the nerolidyl derivative (VII) and farnesyl pyrophosphate (I) we have two reactants which could condense with each other as isopentenyl

pyrophosphate is presumed to do with 3:3-dimethylallyl pyrophosphate or with geranyl pyrophosphate. The intermediate cation (VIII) could then become stabilized by the loss, in successive stages, of a proton, the anion X^-, and another proton, to yield dehydrosqualene (IX), reduction of which to squalene (X) is presumed.

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The significant points of the chemical mechanism of squalene biosynthesis as outlined are: (a) that the process is not a concerted reaction, but proceeds in steps with well defined stable intermediates; (b) that during isomerization of isopentenyl pyrophosphate there is an uptake of one proton in the terminal methylene group and that this proton appears finally in one of the terminal methyl groups at each end of squalene which means the entry into each molecule of squalene of two protons not contained originally in mevalonic acid; (c) that there are no reductive steps involved in the synthesis of geranyl or farnesyl pyrophosphate; (d) that farnesyl pyrophosphate and nerolidyl derivative are the two sesquiterpenoids condensing to the symmetrical dihydrotriterpene squalene, a stable intermediate being dehydrosqualene; (e) that during stabilization of the condensation product of the farnesyl and nerolidyl derivatives elimination of two protons, originally attached to C-5 of mevalonate, occurs and (f) that the final step is a reduction, introducing into squalene two further hydrogen atoms not contained originally in mevalonic acid.

Although further experimental work is needed to establish each of these points unequivocally, supporting evidence for this scheme is already available. The finding in a single liver enzyme preparation of the formation from mevalonate of derivatives of dimethylallyl alcohol, of geraniol, of farnesol and of nerolidol[3] shows that the synthesis of the C_{15} derivatives

is not a concerted reaction, but occurs in steps; for the utilization of the C_{15} compounds for squalene synthesis enzymes attached to microsomes are needed,[1,3] all of which is in accord with postulate (a). The most relevant information concerning postulates (b), (e) and (f) comes from the recent work of Rilling and Bloch[2] who (i) analysed the distribution of deuterium in squalene biosynthesized from [5-$^{2}H_2$-2-^{14}C]mevalonate by a yeast autolysate, and (ii) determined the extent and position of deuterium and tritium labelling in squalene biosynthesized from [2-^{14}C]mevalonate in the presence of $^{2}H_2O$ and $^{3}H_2O$ respectively. They found that out of the 12 possible deuterium atoms which might have been incorporated into squalene from [5-$^{2}H_2$] mevalonate only 10 were contained in the molecule and that the two which disappeared were lost from the two central carbon atoms of squalene. Thus postulate (e) is satisfied. The experiments with heavy water showed on the other hand that during squalene synthesis from mevalonic acid 4 atoms of hydrogen were taken up from the reaction medium, 2 of these were located at the two central carbon atoms and the remainder (which suffered some loss during chemical degradation) in the two terminal isopropyl-groups of squalene. These results support the requirements of points (b) and (f). It should be pointed out, however, that the uptake of hydrogen from the water of the reaction medium during a reductive process depends on the nature of the reducer. Since both in the yeast[1] and in the liver enzyme system[3] reduced pyridine nucleotides are needed for the utilization of farnesyl-pyrophosphate (or of farnesyl- and nerolidyl-pyrophosphate) for squalene synthesis, one might have expected in the experiments of Rilling and Bloch the uptake of only one atom of hydrogen (proton) from the water of the incubation medium instead of the observed two into the centre of

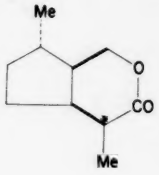
squalene if the reducer was TPNH + H^+, or DPNH + H^+. On the other hand in the experiment quoted a crude enzyme system, fortified with DPN (not DPNH) was used and thus the possibility exists that DPN^{2}H was formed by some indirect mechanism. Some incorporation of deuterium from DPN^{2}H, generated with [1-$^2H_2$] ethanol and alcohol dehydrogenase, into squalene during its biosynthesis from mevalonate was noted in preliminary experiments by Rilling and Bloch,[2] but the values obtained were too low and variable to decide whether DPNH was the immediate reducing agent, or whether it functioned in their system by reducing another coenzyme. In support of the possible existence of dehydrosqualene as an intermediate it might be relevant to mention that in the carotenoid series, in phytoene, the conjugated triene structure is present in the six central carbon atoms.

1959

E R R A T U M

R. H. Jaeger and Sir Robert Robinson, The conversion of D-isoiridomyrmecin into D-iridomyrmecin, Tetrahedron Letters No. 15, 14-18 (1959).

An unfortunate error occurred in the publication of formula I on p. 14 of the above article. The correct formula is reproduced below.



I

1959

Tetrahedron Letters No. 20, pp. 1-6, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE CAMPHOKETENE DIMERS

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Department of Chemistry, Harvard University, Cambridge, Mass.

(Received 27 October 1959)

TREATMENT of an ethereal solution of d-camphor-3-carbonyl chloride (I) with quinoline or triethylamine yields two isomeric products, $C_{22}H_{28}O_4$, which were considered by Staudinger and Schotz[1] to be stereoisomers of the 1,3-cyclobutanedione derivative II, arising by dimerization of "camphoketene" (III). Pyrolysis of these camphoketene dimers or of I gives a third isomer which has been assigned structure IV.[1] We now propose that the camphoketene dimers be assigned structure IV and the pyrolysis product structure V. These proposals serve to rationalize all the previously reported data, including results explicable only with difficulty on the basis of the earlier formulations, and are uniquely in accord with the new data now to be presented.

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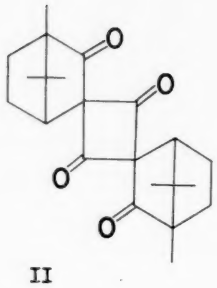
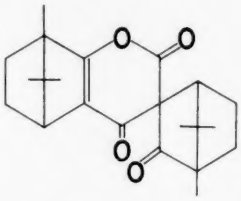
[1] H. Staudinger and S. Schotz, Ber. 53, 1105 (1920).



II



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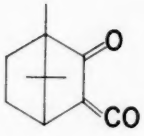
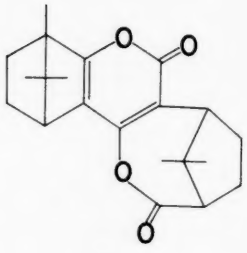


III



V

We find that, as previously reported, the two camphoketene dimers have similar m.p.'s (147.5-149.5°, 150-151.5°) and widely divergent optical rotations [66.3°, 132° (c = 5 in ethyl acetate)] , but that, contrary to the original report, neither compound gives an immediate $FeCl_3$ test. The assignment of the formula $C_{22}H_{28}O_4$ to both compounds has been confirmed (Found: (i) C, 74.24; H, 7.97; M.W., 363 (ii) C, 74.01; H, 7.99; M.W., 388. $C_{22}H_{28}O_4$ requires C, 74.13; H, 7.92; M.W., 356). Their infrared spectra are very similar, showing bands at ca. 5.55, 5.70, 5.96 and 6.18 μ; their ultraviolet spectra show maxima at 297 mμ (ε 5700) and 293 mμ (ε 5300). The close similarity of their spectra corroborates their formulation as stereoisomers. The infrared spectra are incompatible with II but can be interpreted in terms of IV, with assignment of the bands at 5.96 and 6.18 μ to the

αβ-unsaturated ketone system, and those at 5.55 and 5.70 μ to the enol lactone and saturated ketone groups, respectively. The ultraviolet spectra also are incompatible with II but are in accord with IV, as shown by comparison with the spectra of the model compounds VI-VIII, whose structures have been independently established.[2]

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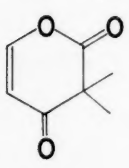
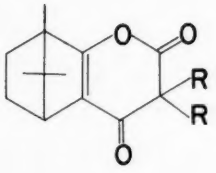


VI

λ_{max}^{EtOH} 250 mμ (ε 7400)



VII R = C_6H_5 λ_{max}^{EtOH} 293 mμ (ε 6700)

VIII R = CH_3 λ_{max}^{EtOH} 282 mμ (ε 7050)

Hydrolysis[1] of either stereoisomer with hydrochloric acid in acetic acid at room temperature gave an acid, m.p. 258-258.5° dec. (Found: C, 70.43; H, 8.04. $C_{22}H_{30}O_5$ requires C, 70.56; H, 8.08), which is now formulated as IX. Its infrared spectrum (λ_{max}^{KBr} 3-4, 5.92, 6.05, 6.17 and 6.45 μ) is compatible with this structure and its ultraviolet spectrum [λ_{max}^{EtOH} 316 mμ (ε 10,000), shifted to 302 mμ (ε 10,000) on addition of NaOH] closely resembles that of the model compound X [2] [λ_{max}^{EtOH} 311 mμ (ε 10,300), shifted to 299 mμ (ε 10,700) on addition of NaOH]. Hydrolysis of IX with hot aqueous potassium hydroxide gave an acid, m.p. 188-189.5°

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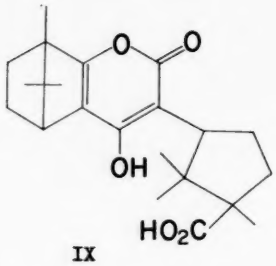
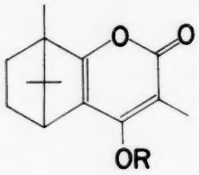
[2] P. Yates and E. A. Chandross, to be published.



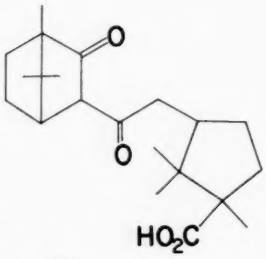
IX



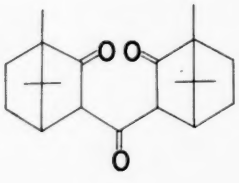
X R = H

XIV R = $COCH_3$

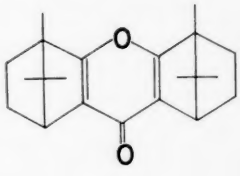
(Found: C, 72.12; H, 9.09. $C_{21}H_{32}O_4$ requires C, 72.38; H, 9.26) which is formulated as XI. Its infrared spectrum [$\lambda_{max}^{CH_2Cl_2}$ 3-4, 5.75, 5.90 (br) and 6.18 μ] and ultraviolet spectrum [λ_{max}^{EtOH} 280 mμ (ϵ 6500), shifted to 313 mμ (ϵ 21,000) on addition of NaOH] resemble those of d-3-isobutyryl-camphor[2] [$\lambda_{max}^{CH_2Cl_2}$ 5.71, 5.86, 5.95 and 6.18 μ; λ_{max}^{EtOH} 279 mμ (ϵ 4970), shifted to 311 mμ (ϵ 22,000) on addition of NaOH]. It reacted with phenyl-hydrazine to give an N-phenylpyrazole derivative, m.p. 216-217° [Found: C, 77.15; H, 8.61; N, 6.72. $C_{27}H_{36}N_2O_2$ requires C, 77.10; H, 8.63; N, 6.66]. Oxidation with alkaline $KMnO_4$ gave a mixture of d-camphoric and d-homocamphoric acids.



XI



XII



XIII

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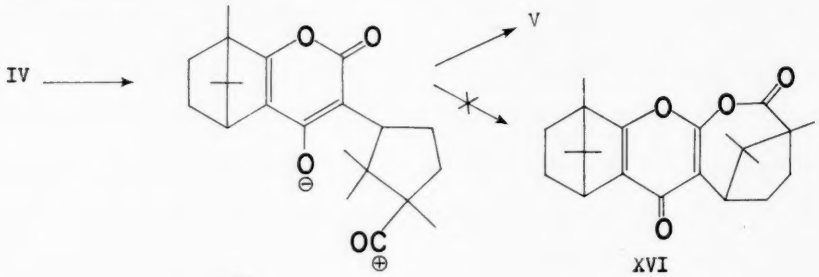
Alkaline hydrolysis of the stereoisomeric dimers with aqueous pyridine gave the triketone XII, obtained by Staudinger and Schotz by hydrolysis with aqueous NaOH.[1] This product, m.p. 183-185° (Found: C, 75.90; H, 9.15. $C_{21}H_{30}O_3$ requires C, 76.32; H, 9.15) showed bands in its infrared spectrum (CH_2Cl_2) at 5.72, 5.90 (br) and 6.16 μ, and λ_{max}^{EtOH} 280 mμ (ϵ 2430), shifted to 318 mμ (ϵ 22,000) on addition of NaOH (cf. the spectra of d-3-isobutyrylcamphor, above). The rates of alkaline hydrolysis of the dimers differed slightly and a tentative assignment of stereochemistry can be made on this basis. Treatment of XII with hot sulfuric acid led to a dehydration product, m.p. 167-168° (Found: C, 80.78; H, 9.03. $C_{21}H_{28}O_2$ requires C, 80.73; H, 9.03), rationally formulable as the γ-pyrone derivative XIII. Its infrared and ultraviolet spectra [$\lambda_{max}^{CH_2Cl_2}$ 6.14, 6.27 μ; λ_{max}^{EtOH} 260 mμ (ϵ 18,300)] are in accord with this formulation.

When I was heated at 160-170° it was converted to a product, m.p. 197-198°, whose formulation as an isomer of the camphoketene dimers was confirmed (Found: C, 73.98; H, 8.13; M.W. 353. $C_{22}H_{28}O_4$ requires C, 74.13; H, 7.92; M.W. 356). The same product was also obtained by heating either camphoketene dimer at 180°. Its infrared spectrum (CH_2Cl_2) shows bands at 5.68, 5.91, 6.13 and 6.39 μ and its ultraviolet spectrum (EtOH) a maximum at 326 mμ (ϵ 9300). The excellent correspondence of these spectra with those of the model compound XIV [2] [$\lambda_{max}^{CH_2Cl_2}$ 5.64, 5.86, 6.15 and 6.38 μ; λ_{max}^{EtOH} 324 mμ (ϵ 10,500)] strongly supports the newly proposed structure, V. Treatment of the pyrolysis product with concentrated hydrochloric acid in the cold led to a mixture of the acids IX and XI; the latter product only was obtained when the reaction was carried out on the steam bath. When IX

was heated in vacuo the pyrolysis product was regenerated. These hydrolysis products serve to confirm V as the structure of the pyrolysis product. Thermal fission of one bond of IV would give the stabilized zwitterion XV, which could recyclize to give either V or the γ-pyrone XVI; the latter is rejected as the structure of the pyrolysis product on the basis of the spectral data.[2]



Acknowledgements - This work was carried out during the tenure of a United States Public Health Service Predoctoral Fellowship by E. A. C. A grant from the William F. Milton Bequest of Harvard University helped to defray the cost of the investigation.

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FORMATION OF 1,4-DIBROMO-2,3-BENZOBIPHENYLENE, 2,3-BENZOBIPHENYLENE, AND 1,2,5,6-TETRABROMO-3,4:7,8-DIBENZOTRICYCLO [4,2,0,$o^{2,5}$] OCTADIENE

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(Received 29 October 1959)

IN recent years there has been considerable interest in derivatives of benzocyclobutene and benzocyclobutadiene.[1,2] Extensive synthetic efforts have been put forth in the preparation of dibenzocyclobutadiene (biphenylene) and its more highly condensed analogs.[3,4,5] This report is concerned with the production of derivatives of benzocyclobutene and

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[1] M. P. Cava and D. R. Napier, J. Amer. Chem. Soc. 80, 2255 (1958) and preceding papers.

[2] M. Avram, D. Dinu and C. D. Nenitzescu, Chem. and Ind. 257 (1959).

[3] W. C. Lothrop, J. Amer. Chem. Soc. 64, 1698 (1942), and preceding paper.

[4] M. P. Cava and J. F. Stucker, ibid. 77, 6022 (1955).

[5] R. F. Curtis and G. Viswanath, J. Chem. Soc. 1670 (1959), and preceding paper.

biphenylene by reaction of α,α,α',α'-tetrabromo-o-xylene (I) with potassium t-butoxide. It was anticipated that 1,1,2-tribromobenzocyclobutene (II) might be a major product of this reaction.

It is well known that tetrabromo-o-xylene (I) yields an intractable polymer when treated with strong aqueous base. o-Phthalaldehyde can be isolated by aqueous hydrolysis in very weakly basic solutions. There have been no studies made, however, on the reaction of tetrabromo-o-xylene with base under anhydrous conditions.

Treatment of I with one mole equivalent of potassium t-butoxide produced none of the expected tribromobenzocyclobutene (II), and approximately half of the starting material was recovered. All of the starting material was converted when seven mole equivalents of base was used and two dimeric products were isolated. The dimers had empirical formulae of $C_{16}H_8Br_2$ and $C_{16}H_8Br_4$ and proved to be 1,4-dibromo-2,3-benzobiphenylene (III) and 1,2,5,6-tetrabromo-3,4:7,8-dibenzotricyclo [4,2,0,$0^{2,5}$] octadiene (IV).[6]

Compound III, yellow needles with m.p. 222-223°, was isolated in 69.2% yield, while the compound IV, white plates decomposing at 214°, accounted for 20.6% of the theoretical yield. The two products were separated by fractional crystallization.

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[6] All compounds gave satisfactory analyses for the formulae shown.

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FIG. 1. Reaction of tetrabromo-o-xylene with strong base and subsequent conversions.

Reduction of III with hydrogen, in the presence of palladium on charcoal and triethylamine, produced β-phenylnaphthalene in 84% yield. Three moles of hydrogen were consumed. This result indicates that III is a dibromo derivative of either 1,2- or 2,3-benzobiphenylene.

The bromine atoms were converted to carboxyl groups in order to determine whether they occupy adjacent positions. By refluxing with excess n-butyl lithium, III was converted to the dilithium derivative. Treatment of the dilithium compound with carbon dioxide, followed by acidification, gave a diacid (V) in a 57.4% yield. The diacid was recovered unchanged after refluxing for 1.5 hr. in acetic anhydride. These results coupled with the information from the reduction reaction indicate that III is 1,4-dibromo-2,3-benzobiphenylene.

Dimer IV was shown to be 1,2,5,6-tetrabromo-3,4:7,8-dibenzotricyclo[4,2,0,$0^{2,5}$]octadiene by the following reactions. Reduction of IV by hydrogen, in the presence of palladium on charcoal and triethylamine, produced 1,2:5,6-dibenzocyclooctadiene (VI) in 92.3% yield. When IV was refluxed in ethanolic sodium iodide solution for two weeks, 35.8% of dimer III and 61.9% of starting material were obtained.

The ultraviolet and infrared spectral data are in accord with the structural assignments of the two dimers. The reactions are summarized in Fig. 1.

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When the dilithium derivative of III was decomposed with methanol, the previously unreported 2,3-benzobiphenylene (VII), m.p. 242.6-243.2°, was obtained in 79% yield. Compound VII was readily reduced with Raney nickel to form β-phenylnaphthalene (95.2%). Cava and Stucker[4] reported that the reduction of 1,2-benzobiphenylene gives 21% of α- and 50% of β-phenylnaphthalene. Treatment of tetrabromo-o-xylene with potassium t-butoxide followed by reaction of III with n-butyl lithium and methanol constitutes a convenient synthesis of 2,3-benzobiphenylene.

Although compound II was not isolated, it is probably an intermediate in the formation of dimer IV. Reaction of II with base would be expected to give 1,2-dibromobenzocyclobutadiene, which would upon dimerization give IV. Dimer III might arise by at least two different types of reactions. One isomer of IV might lose bromine to give III. The Diels-Alder reaction of the compound formed by 1,4-elimination of hydrogen bromide from tetrabromo-o-xylene with 1,2-dibromobenzocyclobutadiene, followed by elimination of hydrogen bromide and loss of molecular bromine would also give dimer III. A full account of the above results will be reported shortly.

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DIE REAKTION ZWISCHEN ALUMINIUMTRIMETHYL UND TITANTETRACHLORID

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(Received 6 November 1959)

DIE Herausgeber dieser Zeitschrift und die Autoren waren beide so liebenswürdig, uns das Manuskript der Mitteilung von Rodriguez, Gabant und Hargitay,[1] zur Kenntnis und Stellungnahme zuzusenden. Wir möchten daraufhin hier das folgende mitteilen:

Das sogenannte "violette Titantrichlorid", wie es aus $TiCl_4$ und Wasserstoff bei hoher Temperatur entsteht, ist gegenüber Aluminiumtrialkylen recht reaktionsträge. Die Reaktionen betreffen daher in der Regel nur mehr oder weniger dicke Schichten an den Oberflächen der Kristalle. Ein vollständiger Umsatz mit Bezug auf $TiCl_3$ ist nicht zu erzielen. Rückschlüsse auf eingetretene Veränderungen sind nur auf dem Wege der indirekten Analysen möglich, und dieses Verfahrens haben sich Rodriguez, Gabant und Hargitay bei ihren Versuchen bedient. "Braunes $TiCl_3$" aus $TiCl_4$ und Wasserstoff in der dunklen elektrischen Entladung oder aus $TiCl_4$ + $ClAlR_2$

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[1] L. Rodriguez, J. Gabant und B. Hargitay, Tetrahedron Letters No. 17, 7 (1959).

hergestellt setzt sich dagegen viel vollständiger mit Aluminiumtrialkylen um. Versuche mit der Reaktion $TiCl_3$ + $Al(CH_3)_3$, die unmittelbar vergleichbar mit denen der genannten Autoren wären, haben wir nicht gemacht, wohl aber haben wir bereits vor drei Jahren die Reaktion zwischen Aluminiumtrimethyl und Titantetrachlorid untersucht. Die Ergebnisse, die einige Beziehungen zur voranstehenden Arbeit haben, sind vor mehr als zwei Jahren in der Dissertation von Stedefeder[2] beschrieben worden.

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Die Reaktion gelingt vollständig, d.h. das Titantetrachlorid verschwindet ganz. Sie ist bei ganz milden Bedingungen (maximal 30°C) möglich, bei denen die Gefahr nachträglicher Veränderungen vermindert sein sollte. Von vielen Versuchen, von denen die Mehrzahl in Lösungen angestellt wurden, wollen wir hier nur zwei - ohne Lösungsmittel - beschreiben. Bei beiden wurde Titantetrachlorid sehr vorsichtig unter intensivem Rühren und unter guter Kühlung in Aluminiumtrimethyl eingetropft und zwar - schon weil anders die Mischung gar nicht rührfähig bleiben würde - das eine Mal in 4, das andere Mal in 12 Mole ("1:4"- bzw. "1:12"-"Versuch" bzw.-"Produkt"). Die Temperatur überstieg nicht + 30°C, die Reaktionszeiten waren 2 bzw. 1,5 Stunden + 2 Stunden Nachrühren. Konform mit dem Zutropfen entwich Methan und zwar 1,84 bzw. 1,9 Mol pro Mol $TiCl_4$. Die Entwicklung hörte praktisch mit der Zugabe des $TiCl_4$ auf. Hinsichtlich der Methan-Mengen stimmen unsere Versuche mit denen von Rodriguez, Gabant und Hargitay[1] etwa überein, wenn man für das eine Chlor im $TiCl_4$ mehr in unseren Versuchen ein zusätzliches Mol Methan rechnet. Anschliessend beseitigten wir alles Flüchtige

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[2] J. Stedefeder, Dissertation Aachen (1957).

im Hochvakuum bei maximal +30°C bis zum konstanten Gewicht des Rückstands.

Trotz der sehr milden Bedingungen der Herstellung stimmte die Zusammensetzung der Rückstände auf keine bestimmte Formel. Für das "1:4-Produkt" fanden wir:

	Al	$Ti_{(gesamt)}$	Cl	C	H	Summe
Proz.	11.5	29.1	39.0	13.9	2.73	96.23
Atome	1	1.42	2.60	2.72	6.4	

Das "1:12"-Produkt hatte eine ähnliche Zusammensetzung, enthielt jedoch etwas mehr organische Anteile und einige Prozente weniger Chlor.

Eine bestimmte Korrelation bestand weder zwischen dem in den festen Rückstand eingegangenen Aluminium und dem Chlor (als $(CH_3)_2AlCl$) im Destillat ("1:4-Produkt": 1:2.6, "1:12-Produkt": 1:3.25) noch etwa zwischen dem bei der Reaktion anfangs entwickelten Methan und dem Chlor im Destillat: 1:1,14 ("1:4-Produkt") bzw. 1:1,28 ("1:12-Produkt"). Pro $TiCl_4$ erscheinen 2,06 bzw. 2,54 Mole $(CH_3)_2AlCl$ im Destillat. Die Stoffbilanz stimmte bei allen Versuchen.

Rodriguez, Gabant und Hargitay[1] haben sich nicht mit der Reduktionswirkung ihrer Produkte gegenüber $FeCl_3$ befasst. Wir haben unsere "schwarzen Katalysatoren" nach der kürzlich beschriebenen Titrationsmethode[3] untersucht und festgestellt, dass sie wesentlich mehr $FeCl_3$ reduzieren, als der in ihnen enthaltenen Menge Ti als Ti^{III} entspricht. Bezeichnet man den stärker reduzierenden Anteil als Ti^{II}, so enthielt unser "1:4-Produkt" 12,25% Ti^{II} neben 16,75% Ti^{III}, mithin Ti^{II}:Ti^{III} = 1:1,36, das "1:12-Produkt" dagegen 14,2% Ti^{II} neben 14,6% Ti^{III}, mithin Ti^{II}:Ti^{III} sehr nahe = 1:1.

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[3] H. Martin und J. Stedefeder, Liebigs Ann. 618, 17 (1958).

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Dies entspricht den Resultaten einer sehr grossen Anzahl von Versuchen mit den verschiedensten Aluminiumtrialkylen bzw. Dialkyl-aluminium-hydriden, bei denen als eine Art Grenze oder besser Haltepunkt der Reduktion des $TiCl_4$ über einen ziemlich grossen Bereich der Variation der Versuchsbedingungen hinweg immer wieder ein Verhältnis $Ti^{II}:Ti^{III} \approx 1$ von uns festgestellt worden ist. Dies scheint uns ähnlich bemerkenswert wie andererseits die Tatsache, dass die Reaktion zwischen $TiCl_4$ und Stoffen der Art R_2AlCl über einen ähnlich weiten Bereich der Bedingungen hinweg nie unter die Wertigkeitsstufe Ti^{III} herunterführt. Da man hochaktive Polyäthylenkatalysatoren nach beiden Prinzipien (mit AlR_3 und mit $R_2AlHalogen$) herstellen kann, und da auch Katalysatoren mit der Kombination $Ti^{III} + Ti^{IV}$ gesichert sind, so ist die Vorstellung, wie sie in einigen vor kurzem erschienenen Patentschriften[4] entwickelt worden ist, die - wenigstens teilweise - Reduktion unter die Wertigkeitsstufe 3 des Titans sei für die Wirkung der Katalysatoren notwendig, sicher in dieser Form falsch.

Andererseits kann aber auch gar keine Rede davon sein, Katalysatoren aus Aluminiumtriäthyl und Titantetrachlorid enthielten so wenig Ti^{II}, wie dies kürzlich Malatesta[5] angegeben hat. Dessen Ergebnisse können mit der von uns beobachteten Erscheinung zusammenhängen, dass sich "schwarze Katalysatoren", die gegenüber $FeCl_3$ eine über Ti^{III} stark hinausgehende

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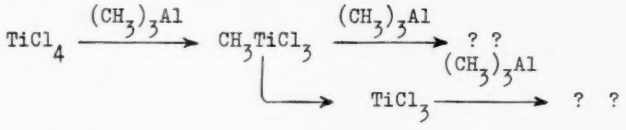
4a U. S. Pat. 2.905645 v. 22.9.1959, U. S. Prior. 16.8.1954. E. J. DuPont de Nemours & Co. (A. W. Anderson, J. Macmillan Bruce, N. G. Merckling und W. L. Truett); b Brit. Pat. 778639 v. 3.8.1955. U. S. Prior. 16. u. 30.8.1954; 10., 21. u. 30.9.1954; 22.11.1954. Du Pont de Nemours & Co.

5 A. Malatesta, Canad. J. Chem. 37, 1176 (1959).

Reduktionswirkung besitzen, sich hinsichtlich der Wasserstoffentwicklung bei der Zersetzung mit Wasser, insbesondere unter milden Bedingungen, verschieden verhalten können, so dass aus der Wasserstoffentwicklung allein kein sicherer Rückschluss auf das Vorliegen der besonderen Reduktionswirkung in den Katalysatoren möglich ist. Diese Reduktionswirkung anders zu erklären als durch die Annahme des Vorhandenseins von Ti^{II}, sehen wir vorläufig keinen zwingenden Grund.

Im übrigen sei auf die Publikation von Martin und Stedefeder[3] verwiesen, in der gezeigt wird, wie der Ti^{II}-Gehalt der "schwarzen Katalysatoren" mit dem Verhältnis Al:Ti zunimmt. Nur bei einem Versuch mit $Al(C_2H_5)_3$: $TiCl_4$ = 0,5:1 fehlte Ti^{II} gänzlich, aber schon bei Al:Ti = 1:1 war deutlich Ti^{II} (3,3%) nachweisbar und diese Menge stieg schliesslich auf rund 50% für Al:Ti >2.

Wir wollen uns hier nicht im einzelnen über die sich möglicherweise abspielenden Reaktionen äussern. Man wird sich jedoch mit der Frage beschäftigen müssen, ob die Komplexität der "schwarzen Katalysatoren" nicht vielleicht damit zusammenhängt, dass es mehrere Wege des Reaktionsverlaufs gibt, z.B. lässt sich an eine Reaktionsverzweigung



denken, die durch die Auffindung des Methyltitanchlorids und seiner spontanen Zersetzung unter Bildung von $TiCl_3$ durch Beermann[6] nahegelegt

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[6] DAS 1023766 v. 16.12.1955. Farbwerke Hoechst A.G. (C. Beermann, H. Bestian und R. Graf).

wird. Die Endprodukte der beiden Reaktionswege brauchen nicht gleichartig zu sein. Dies sei zunächst nicht mehr als ein Schema. Es mag weitere, ähnliche geben. Zur Kennzeichnung der Natur der "schwarzen Katalysatoren" scheint uns das Ergebnis ihrer Zersetzung mit schwerem Wasser nicht unwichtig. Rodriguez, Gabant und Hargitay[1] machen einige Andeutungen hierüber. Wir haben diese Reaktion bereits vor drei Jahren studiert und in der schon erwähnten Dissertation Stedefeder 1957 beschrieben.

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Das Volum Gas, das wir bei diesen Versuchen erhielten, entsprach 95% dessen, was man auf Grund des C- und H-Gehalts der "schwarzen Katalysatoren" erwarten sollte. Wir stellten massenspektrometrisch folgende Zusammensetzung fest:

	CH_4	CH_3D	CH_2D_2	CHD_3	CD_4	$C_2C_3C_4$ Kohlenwasserstoffe*	D_2	HD
"1:4-Produkt":	3,2	74,1	3,2	1,9	9,5	5	2**	0,4
"1:12-Produkt":	5,0	70,1	3,4	2,5	10,6	5	3**	0,5

* zum Teil deuteriert.

** die Deuterolyse wurde unter Bedingungen ausgeführt, bei denen die spontane Oxydation des Ti^{II} unter H_2- bzw. D_2-Entwicklung noch nicht vollständig verläuft.

Diese Zahlen bedeuten folgendes:

70-74% des Kohlenstoffs sind an Metall gebundene CH_3-Gruppen, 5-6% liegen als $>CH_2$ + $\geqslant CH$-Gruppen und ungefähr 10% in Form von "Carbidgruppen" $>C<$ vor. Der hohe Gehalt an diesen letzten ist sehr bemerkenswert. Irgendwie wesentlich fehlerhaft kann dies Ergebnis nicht sein, denn gerade beim CD_4 arbeitet das Massenspektrometer recht genau. Beachtet man, dass auch 3-5% nichtdeuteriertes Methan entstanden, d.h. wesentlich mehr als dem HOD-Gehalt unseres schweren Wassers entsprachen, so möchte man

fast vermuten, dass der ursprünglichen Deuterolyse noch ein etwa durch unsere Katalysatoren oder deren Zersetzungsprodukte katalysierter Wasserstoff-Deuterium-Austausch überlagert ist. Nach der Zusammensetzung der Gase mussten dann die Vorgänge

$$2\ CH_3D \rightleftharpoons CH_4 + CH_2D_2 \qquad \text{und}$$

$$CH_3D + CD_4 = CH_2D_2 + CHD_3$$

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am häufigsten sein, dabei der erste häufiger als der zweite. Tatsächlich stimmt dies qualitativ. Auch entsprechen sich CH_4 und CH_2D_2 erwartungsgemäss der Menge nach ungefähr. Anzeichen für eine solche Katalyse des Austauschs haben wir in besonderen Versuchen tatsächlich festgestellt. Hiernach müsste der Kohlenstoff in den ursprünglichen schwarzen Katalysatoren ganz überwiegend in Form von $-CH_3$-Gruppen einerseits, $\rangle C\langle$ -Gruppen andererseits vorgelegen haben. $\rangle CH_2$- und $\rangle CH$-Gruppen wären, wenn überhaupt, jedenfalls in geringerer Menge als zusammen 5% vorhanden. Das bei der Reaktion $Al(CH_3)_3 + TiCl_4$ frei werdende Methan kann sich bilden
(1) dadurch, dass Methylradikale ihrer Umgebung Wasserstoff entreissen,
(2) aus Metall-methylen durch Abspaltung von Methan gemäss

$$2\ MCH_3 = CH_4 + M_2CH_2$$

$$3\ MCH_3 = 2\ CH_4 + M_3CH$$

$$4\ MCH_3 = 3\ CH_4 + M_4C. \quad (M = \text{Metalläquivalent}).$$

Solche Reaktionen - sie entsprechen Vorgängen wie etwa

$$Al(OH)_3 = HOAlO + H_2O \qquad \text{und}$$

$$2\ Al(OH)_3 = Al_2O_3 + 3\ H_2O \quad -$$

sind für Methyllithium und Dimethyl-magnesium schon beschrieben,[7] sie sind

auch charakteristisch für $Al(CH_3)_3$ bei 200° und darüber, wie in Kürze an anderer Stelle publiziert werden wird. Wenn solche Reaktionen bei Methyl an Titan viel leichter einträten als am Aluminium, so wäre damit beides, die Abspaltung von Methan (oder eines Teils desselben) und das Vorhandensein von Carbid-Gruppen erklärt. Es wäre auch verständlich, warum die Zwischenglieder - Methylen- und Methin-Gruppen - so auffallend schwach vertreten sind. Aufzuklären bliebe der Verlauf des Übergangs von Ti^{III} in Ti^{II} bzw. - wenn man an Ti^{II} "nicht glaubt" - die Natur und Bildungsweise desjenigen Stoffanteils in den "schwarzen Katalysatoren", dem die über das Ti^{III} hinausgehende Reduktionswirkung zukommt.

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[7] K. Ziegler, K. Nagel und M. Patheiger, Z. Anorg. Chem. 282, 345 (1955).

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1959

A TOTAL SYNTHESIS OF dl-EBURNAMONINE

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(Received 9 November 1959)

WE have recently described the isolation and determination of the structure of four alkaloids from Hunteria eburnea Pichon.[1] It was shown how they could be interconverted, eburnamonine (I) being the key compound and their relationship to aspidospermine (II)[2] was pointed out. Both (I) and (II) appear to have been formed from a tryptamine moiety plus a residue (III) either by an α-type condensation[3] in the case of (I) or a β-type for (II). The fragment (III) is patently a C_6-C_2-C_1 unit derived from a one carbon source[4] and an aromatic precursor such as dopa which undergoes fission[5] at some stage. Alternatively (III) may have had its genesis in a hydroaromatic compound such as prephenic acid.[6]

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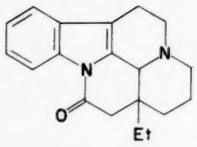
[1] M. F. Bartlett, W. I. Taylor and Raymond-Hamet, C. R. Acad. Sci., Paris 249, 1259 (1959).

[2] J. F. D. Mills and S. C. Nyburg, Tetrahedron Letters No. 11, 1 (1959).

[3] For the use of these terms see R. Robinson, Structural Relations of Natural Products p. 100 et seq. Clarendon Press (1955); the biogenetic ideas elaborated in this note have also been considered by Sir Robert Robinson (private communication of a brief note submitted to Tetrahedron Letters).



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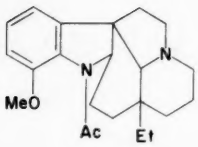
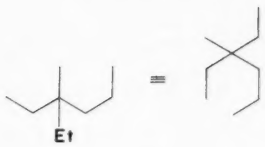


II



III

We have carried out a total synthesis of eburnamonine which although starting from p-ethylphenol can be regarded as a formal model for either of the routes alluded to above. p-Ethylphenol subjected to a Reimer - Tiemann reaction furnished 4-dichloromethyl-4-ethyl-cyclohexa-2:5-dienone, m.p. 61-62° (Found: C, 53.0; H, 5.0. $C_9H_{10}OCl_2$ requires: C, 52.7; H, 4.9) which with palladium-charcoal in ethanol yielded 4-dichloromethyl-4-ethylcyclohexanone, m.p. 58° (Found: C, 51.5; H, 6.8. $C_9H_{14}OCl_2$ requires: C, 51.6; H, 6.7). Oxidation of the latter compound with concentrated nitric acid gave β-dichloromethyl-β-ethyladipic acid, m.p. 126° (Found: C, 42.0; H, 5.5. $C_9H_{14}O_4Cl_2$ requires: C, 42.0; H, 5.5). Heating an aqueous solution of the dicarboxylic acid in a sealed tube at 200° gave the aldehydo-diacid (V), characterized as the γ-lactone (IV), m.p. 102-3° (Found: C, 53.4; H, 7.0. $C_9H_{14}O_5$ requires: C, 53.5, H, 7.0). Upon heating the lactone with

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4 Perhaps the same one that yields the C_{21} carbon of yohimbine.

5 R. B. Woodward, Nature, Lond. 162, 155 (1948).

6 For a comprehensive review on this subject see E. Wenkert, Experientia 15, 165 (1959).

tryptamine in dilute aqueous hydrochloric acid eburnamonine lactam (VI) was obtained in 5-10% yield, m.p. 217° (Found: C, 73.7; H, 6.7. $C_{19}H_{20}O_2N_2$ requires: C, 74.0; H, 6.5). The lactam was reduced quantitatively by lithium aluminium hydride in ether to a mixture of eburnamine (VII) and iso-eburnamine (VII) which was oxidized directly with chromic oxide in pyridine to dl-eburnamonine (I) in very high yield, m.p. 203-4° (Found: C, 77.3; H, 7.7. $C_{19}H_{22}ON_2$ requires: C, 77.5; H, 7.5). Its infrared spectrum measured in a Nujol mull was indistinguishable from that of a similarly prepared sample of eburnamonine.

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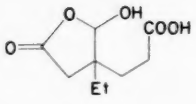

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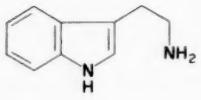

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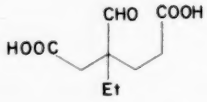

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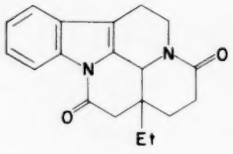
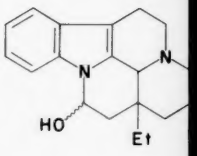


VI



VII

Tetrahedron Letters No. 20, pp. 23-28, 1959. Pergamon Press Ltd. Printed in Great Britain.

A USEFUL MODEL FOR THE OPTICAL ACTIVITY OF DEUTERIUM COMPOUNDS[1]

James H. Brewster

Department of Chemistry, Purdue University, Lafayette, Indiana

(Received 28 October 1959)

THE empirical Conformational Asymmetry Rule[1,2] permits the assignment of absolute configuration to a number of compounds having both deuterium and hydrogen at the asymmetric center; these configurations are consistent with those assigned on mechanistic grounds.[3] Thus, butane-2-d, in the indicated absolute configuration,[4] would have the three staggered

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[1] J. H. Brewster, J. Amer. Chem. Soc. 81, 5475 (1959).

[2] The skew system of atoms shown below in Newman projection is dextrorotatory and contributes $k \cdot X \cdot Y$ to $[M]_D$; the constants X and Y appear to be functions of the refractions of atoms X and Y. The atomic refraction of deuterium is less than that of hydrogen; thus the molecular refraction of hexadeutero-benzene is 0.144 lower than that of benzene; C. K. Ingold, C. G. Raisin and C. L. Wilson, J. Chem. Soc. 915 (1936). On this basis, $k \cdot X \cdot D$ will be smaller than $k \cdot X \cdot H$.

conformations (I_{a-c}) for which molecular rotations would be predicted[2] as shown. Letting the fractional concentration of each gauche form be x, the molecular rotation of a mixture of these three conformations can be expressed:

$$[M]_D = (1-3x)\ k\ (C - H)\ (H - D) \qquad (1)$$

Since the trans form (Ia) predominates, x must be less than 1/3 and expression (1) must be positive. This being the sole expected[1] source of optical activity in this case, we may equate expression (1) with the observed molecular rotation: $[M]_D = + 0.33 \pm 0.01^{\circ}$.[3,4] A parallel analysis indicates that 1-phenylbutane-1-d (II) should be ca. 0.33° more dextrorotatory than 1-phenylethane-1-d (III) in the configurations shown; this could occur only if both were dextrorotatory[5] (observed difference: $M_{II} - M_{III} = + 0.27 \pm 0.11^{\circ}$). Similarly, the O-alkyl and O-acyl derivatives of benzyl-α-d alcohol (IV) and butanol-1-d (V) should be more dextrorotatory than the parent alcohols[6] in the indicated configurations (O forward); these configurations are the same as those assigned by Streitwieser[3] to the compounds having the rotations shown. The complete agreement between these configurational assignments and those made on mechanistic grounds suggests that this rule can be used to assign an absolute configuration to

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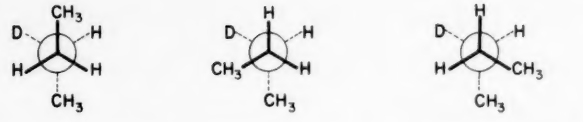
[3] A. Streitwieser, Jr., J. R. Wolfe, Jr. and W. D. Schaeffer, Tetrahedron 6, 338 (1959).

[4] This configuration has been assigned to the (+) isomer; G. K. Helmcamp, C. D. Joel and H. Sharman, J. Org. Chem. 21, 844 (1956).

[5] These absolute configurations have been assigned to the (+) isomers by E. L. Eliel, J. Amer. Chem. Soc. 71, 3970 (1949) (II) and by Streitwieser[3] on mechanistic grounds.

ethanol-1-d.[7]



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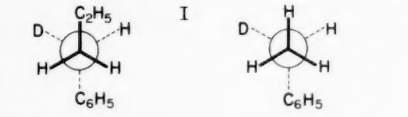

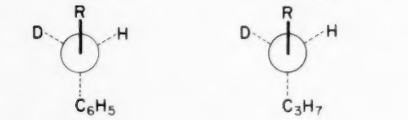

R	$[M]_D^3$
-H	-0·780 ± 0·002
$-C_2H_5$	-0·132 ± 0·004
Acetyl	-0·260 ± 0·006
Acid phthalate	+0·538 ± 0·013

IV

R	$[M]_D^3$
-H	-0·139 ± 0·014
Acetyl	+0·56 ± 0·04
$-SO_2C_6H_4NO_2$	+0·332 ± 0·093
$-SO_2C_6H_4Br$	+0·224 ± 0·046
Acid phthalate	+0·85 ± 0·11

V

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6 We may estimate the magnitude of these shifts by assuming that the steric requirement of a pair of unshared electrons is approximately that of a hydrogen atom. If so, there will be little or no conformational asymmetry about the C*-O bond in the alcohols while the conformational asymmetry in the derivatives will resemble that in I. The rotatory effect of the unshared electron pairs (E) is estimated from the constant (Part II):[1]

$$k\,(C - H)\,(H - E) = +\,50$$

as follows:

$$\Delta\,[M] = (1 - 3x)\,k\,(R - E)(H - D)$$

On the present basis, butanol-1-d (VIb) should be ca. 0.33° more dextrorotatory than ethanol-1-d (VIa) in the indicated configurations. Here the magnitudes of rotation indicate that the configurationally related alcohols have opposite signs of rotation, contrary to the assumption of Levy, Loewus and Vennesland.[7]

As seen in VII, the original Atomic Asymmetry Rule[1,8] gives correct predictions in five of the seven systems to which it might be applied. Apparently, however, the hydroxy and amino groups must be assigned

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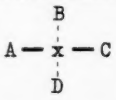
$$= (1 - 3x)\left[k(C - H)(H - E) + k(C - H)(R - H)\right] \frac{k\,(C - H)(H - D)}{k\,(C - H)(C - H)}$$

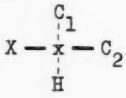
On this basis, when R is alkyl $\Delta[M]$ is ca. + 0.60°, when R is acetyl $\Delta[M]$ is ca. + 0.77°. These values are reasonably close to those observed. The large shifts shown by the acid phthalates suggest that the phenyl group contributes to the rotation too.

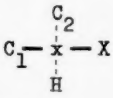
7 H. R. Levy, F. A. Loewus and B. Vennesland, J. Amer. Chem. Soc. 79, 2949 (1957).

8 An asymmetric atom is dextrorotatory in the configuration:



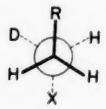
when the four attachment atoms can be ranked: A > B > C > D in accord with the sequence: I > Br > SH > Cl > CN > C_6H_5 > CO_2H > CH_3 > NH_2 > OH > H > D. It was pointed out in Part I that unique assignments of rotational rank could not (at that time) be made to the hetero substituents (other than Cl) but that each must either rank above the carbon sequence or between that sequence and hydrogen. This ambiguity arises because the two configurations:



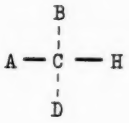


are identical; rotational rank was therefore assigned on the basis of conformational rotatory power and atomic refraction. Such ambiguity does not occur in compounds of series VII; by using these compounds A can unambiguously be assigned a higher rank than B when configuration VII is dextrorotatory.

rotational rank higher than the carbon sequence when they are α- to a phenyl group. This amendment of the empirical Atomic Asymmetry Rule necessitates no changes in the treatment of the compounds considered in Part I, except for the case of (+) atrolactic acid (VIII) where the amended rule indicates that the asummetric atom makes a positive contribution to $[M]_D$. It is, perhaps, pertinent in this regard to point out that the phenyl group is reported not to produce rotation anomalies near its absorption band at about 265 mμ in hydrocarbons and acids[9] but does produce



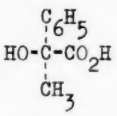
VI



VII

	R	X	$[M]_D$[3]
a.	H	OH	-0.13 ± 0.02
b.	C_2H_5	OH	+0.139 ± 0.014
c.	C_2H_5	NH_2	-0.028 ± 0.009*
d.	C_2H_5	Cl	+0.37 ± 0.03

A	B	$[M]_D$[3]
CH_3	OH	+0.13 ± 0.02
CH_3	NH_2	ca. +0.33**
Cl	CH_3	ca. +0.07**
C_6H_5	CH_3	+0.78 ± 0.06
Br	C_6H_5	+1.06 ± 0.34
OH	C_6H_5	+0.780 ± 0.002
NH_2	C_6H_5	+1.110 ± 0.016



VIII

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* Calculated from the data of A. Streitwieser, Jr. and W. D. Schaeffer, J. Amer. Chem. Soc. 78, 5597 (1957), assuming the value shown above for optically pure alcohol.

such anomalies in the α-phenylethyl amines and alcohols[10,11] and in certain β-phenylethyl alcohols as well,[12] suggesting the occurrence of a rotationally significant interaction of hetero substituents with phenyl groups.

** Estimated from rotations given in VI, letting expression (1)=0.30.

9 A. Rothen and P. A. Levene, J. Chem. Phys. 7, 975 (1939).

10 G. G. Lyle, Abstracts of Papers, 136th Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, p. 71P.

11 J. H. Brewster, S. F. Osman and G. Asato, unpublished.

12 J. L. Mateos and D. J. Cram, J. Amer. Chem. Soc. 81, 2756 (1959).

1959

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Tetrahedron Letters No. 21, pp. 1-4, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

METHINFARBSTOFFE METALLORGANISCHER VERBINDUNGEN

DIFERROCENYLMETHIN-PERCHLORAT

C. Jutz

Organisch-chemisches Institut, Technische Hochschule Munchen

(Received 6 November 1959)

NACH neueren Arbeiten reagiert der Vilsmeier-Primärkomplex[1,2] aus N-disubstituiertem Formamid und Lewis-Säure - z.B. N-Methylformanilid/$POCl_3$ - nach einem S_E-Mechanismus mit einer nucleophilen Komponente unter Bildung eines resonanzstabilisierten Immonium-Kations. In zahlreichen Fällen lässt sich dieses Ion aus der Reaktionslösung als Salz (Perchlorat, Fluoroborat) isolieren; die Hydrolyse ergibt die Formylverbindung (Aldehyd). Als nucleophile Partner lassen sich auch, wie wir fanden, quasiaromatische, metallorganische Verbindungen, z.B. Ferrocen (Di-cyclopentadienyl-eisen), einsetzen. So färbt sich die Benzol-Lösung von Ferrocen und Methylformanilid/$POCl_3$ nach mehreren Stunden durch die gebildeten Ferrocenal-

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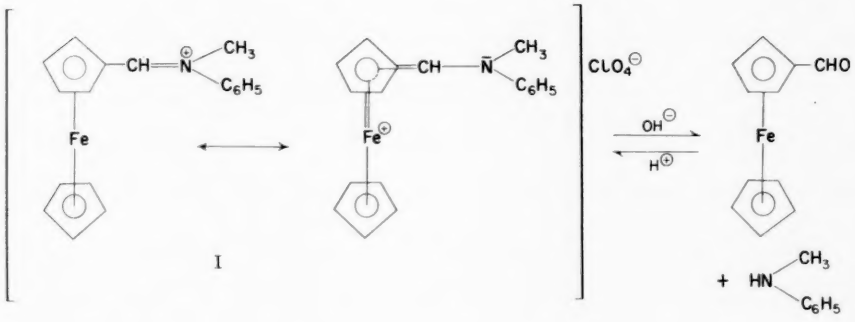
[1] C. Jutz, Südwestdeutsche Chemiedozenten-Tagung, Karlsruhe, Oktober, 1956; Angew. Chem. 69, 104 (1957); Chem. Ber. 91, 850 (1958).

[2] H. Bredereck, R. Gompper, K. Klemm und H. Rempfen, Chem. Ber. 92, 837 (1959); Z. Arnold und Mitarbeiter, Coll. Czech. Chem. Comm. 23, 457 (1958); 24, 2379 (1959); 24, 2385 (1959); B. Eistert und F. Haupter, Chem. Ber. 92, 1922 (1959).

dehydmethylanil-Ionen tief violettrot. Aus der Reaktionslösung wurde das Ferrocenaldehyd-methylanil-perchlorat (I), nach Hydrolyse Ferrocenaldehyd[3] isoliert. Aus dem Aldehyd, Methylanilin und Säure bildete sich umgekehrt das Farbsalz I praktisch quantitativ wieder. I: $C_{18}H_{18}NFe.\ ClO_4$ (403.6) ber. C 53.56 H 4.50 gef. C 53.27 H 4.35 Braunschwarze, glänzende Nadeln aus Chloroform/n-Hexan; verpufft beim Erhitzen; zersetzt sich in allen Lösungsmitteln mit Hydroxylgruppen unter Abscheidung unlöslicher, braunschwarzer Niederschläge. λ_{max} bei 515 mμ und 372.5 mμ in Chloroformlösung.



I

In weiterer Übereinstimmung mit Ergebnissen rein organischer Verbindungen - Synthese von Methin- und Polymethin- Farbstoffsalzen nach Art der Vilsmeier-Reaktion[4] - konnte aus Ferrocen und Ferrocenaldehyd

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[3] M. Rosenblum, Chem. & Ind. 72 (1957); J. M. Osgerby und P. L. Pauson, Chem. & Ind. 209 (1957).

[4] K. Hafner, Angew. Chem. 70, 413 (1958); C. Jutz, Chem. Ber. 91, 856 (1958) (Fussnote) und Südwestdeutsche Chemiedozenten-Tagung, Tübingen, April 1959; Angew. Chem. 71, 380 (1959).

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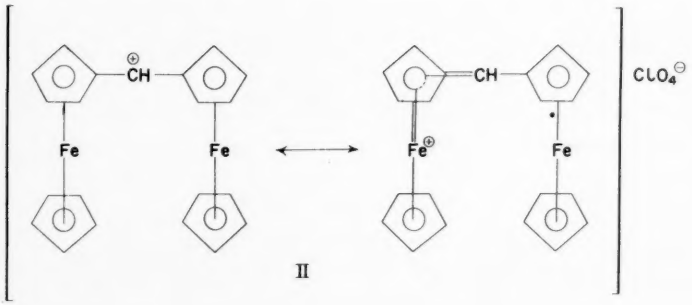
Diferrocenylmethin-perchlorat (II) dargestellt werden. Das tiefblaue Diferrocenylmethin-Kation bildet sich auch direkt aus Ferrocen in Ameisensäure mittels einer Lewis-Säure unter Ausschluss von Luftsauerstoff. Lösungen von II-Salzen in Chloroform hellen sich beim Schütteln mit wässriger Sodalösung nach Hellgelb auf (Diferrocenyl-carbinol).

II: $C_{21}H_{19}Fe_2.ClO_4$ (482.5) ber. C 52.27 H 3.96 gef. C 52.62 H 3.91. Schwarze Nädelchen mit Bronze-Glanz aus Chloroform/n-Hexan; verpufft sehr heftig beim Erhitzen. In Lösungsmitteln mit Hydroxylgruppen tritt ebenfalls langsam Zersetzung ein. Das, dem Farbstoff II entsprechende, Diferrocenyltrimethin-perchlorat wurde inzwischen auch dargestellt. Die grüne Lösung desselben in CH_2Cl_2 zeigt ein sehr ähnliches Spektr. mit λ_{max} bei 785 mμ und 425 mμ.

λ_{max} 605 mμ und 352 mμ (lg ε 3.89, 4.13); λ_{min} 830 mμ, 440 mμ und 300 mμ (lg ε 3.14, 3.22, 3.73), lg ε 3.58 bei 1000 mμ und lg ε 4.20 bei 230 mμ in Chloroformlösung.

I.R.-Spektrum: (KBr-Pressling) mit ausgeprägt scharfen Schwingungsbanden bei (cm^{-1}): 652, 668, 749, 826, 834, 840 (stark), 885, 911, 943,



II

1005, 1036, 1054, 1099 (stärkste Bande mit Überlagerungen), 1120, 1142, 1264, 1321, 1348, 1366, 1396, 1412, 1531 (zweitstärkste Bande), 1613, 2045 (relativ schwache Bande), 2899 (relativ schwache Bande), 3058. Identisch mit dem Spektrum des Ferrocens ist die Schwingung bei 1099 cm^{-1}, andere Schwingungsbanden sind nach höheren und niedrigeren Frequenzen verschoben, viele im Ferrocenspektrum nicht vorhanden. Wie erwartet, ist II diamagnetisch ($\chi_M^{295.5^\circ K}$ $-79.1 \pm 1.5\% \cdot 10^{-6} cm^3 Mol^{-1}$).

Für die Erklärung des Reaktionsmechanismus' und der Struktur des Kations II ist die Tatsache von Bedeutung, dass in allen bisher bekannten Fällen ein induktiver (+I)-Effekt der nucleophilen Komponente allein die Vilsmeier-Reaktion nicht ermöglicht. Vielmehr ist eine Stabilisierung des ersten Reaktionsproduktes durch Mesomerie notwendig. Die somit zu fordernde Mesomerie[5] von I und II lässt sich nach der üblichen Schreibweise durch Grenzformeln nur unbefriedigend ausdrücken. Die Einbeziehung des Fe-Atoms in das mesomere System ohne Änderung der Multiplizität würde jedoch einige formale Schwierigkeiten beheben.

Verbindungen verwandter Art, sowie gemischt organisch-metallorganische Methinfarbstoffsalze werden z.Zt. untersucht.

Folgenden Herren sei an dieser Stelle besonders gedankt: Priv.-Doz. Dr. H. Simon und Frl. Pflaumer (Spezialanalyse), Dipl. Chem. H. Schnith (Aufnahme optischer Spektren), Prof. Dr. E. O. Fischer (I.R.-Spektren), und Dipl. Chem. Th. Kruck (magnetische Wägung). Durch eine Sachbeihilfe der Deutschen Forschungs Gemeinschaft wurde die Arbeit unterstützt.

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[5] R. B. Woodward und Mitarbeiter, J. Amer. Chem. Soc. 74, 3458 (1952); A. N. Nesmejanov und Mitarbeiter, sowie zahlreiche Arbeiten anderer Forscher. Vgl. dazu auch die Vortragsreferate, IUPAC-Tagung, München, August/September, 1959, Nr. A 144, A 145, A 146, A 147.

Tetrahedron Letters, No. 21, pp. 5-6, 1959. Pergamon Press Ltd. Printed in Great Britain.

1959

THE SYNTHESIS OF PACHYRRHIZIN

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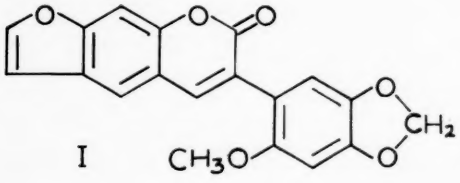
Department of Chemistry, New York University, New York 3, N. Y.

(Received 13 November 1959)

WE wish to report the synthesis of pachyrrhizin (Norton and Hansberry's[1] "compound III") confirming the structure (I) assigned to it by Schmid and coworkers.[2]



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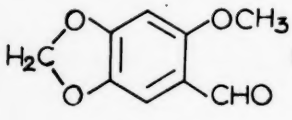

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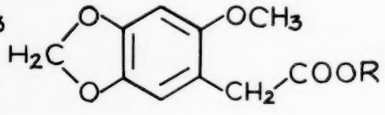
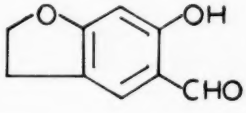


IIIa, R=H

b, R=CH_3



IV

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[1] L. B. Norton and R. Hansberry, J. Amer. Chem. Soc. 67, 1609 (1945).

[2] E. Simonitsch, H. Forei and H. Schmid, Monatsh. 88, 541 (1957).

2-Methoxy-4, 5-methylenedioxyphenylacetic acid (IIIa; m.p. 97-98°. Found: C, 57.3; H, 4.8. $C_{10}H_{10}O_5$ requires: C, 57.1; H, 4.8%), obtained from 2-methoxy-4, 5-methylenedioxybenzaldehyde (II)[3] through the azlactone (m.p. 273-274°. Found: C, 66.6; H, 4.2; N, 4.3. $C_{18}H_{13}O_5N$ requires: C, 66.9; H, 4.1; N, 4.3%), was converted into its methyl ester (IIIb) and then condensed with 5-formyl-6-hydroxycoumaran (IV)[4] in the presence of piperidine to give dihydropachyrrhizin[2] (m.p. 215-216°). This, on dehydrogenation by the N-bromosuccinimide-dimethylaniline method of Geissman and Hinreiner,[5] afforded pachyrrhizin (I; m.p. 207-208°) identical with an authentic sample of the natural product as shown by the two infrared spectra and the absence of depression of a mixture melting point.

Full details of this work will be published shortly.

Acknowledgements — We should like to express our thanks to Prof. H. Schmid, Zurich, for kindly providing us with a sample of natural pachyrrhizin and to Mr. J. Cazes of this department for determining the infrared spectra.

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[3] K. N. Campbell, P. F. Hopper and B. K. Campbell, J. Org. Chem. 16, 1736 (1951).

[4] J. S. H. Davies, P. A. McCrea, W. L. Norris and G. R. Ramage, J. Chem. Soc. 3206 (1950).

[5] T. A. Geissman and E. Hinreiner, J. Amer. Chem. Soc. 73, 782 (1951).

Tetrahedron Letters No. 21, pp. 7-9, 1959. Pergamon Press Ltd. Printed in Great Britain.

AN ACID STABLE CYCLOHEXADIENONE

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Department of Chemistry, Smith College, Northampton, Mass. and The Children's Cancer Research Foundation, Boston, Mass.[1]

(Received 10 November 1959)

1959

The susceptibility of cyclohexadienones to change in acidic media has been the subject of numerous studies.[2] Data sufficient to outline a detailed mechanism for the change from dienone to phenol have been presented.[2 c,h] In this note the synthesis of an acid stable cyclohexadienone is reported. The absorption spectrum of a species closely related to the postulated initial intermediate of the dienone-phenol rearrangement is determined.

Protonation of the oxygen atom of a cyclohexadienone with concomitant formation of the delocalized ion (I) will be mirrored by the appearance of a new maximum in the ultraviolet region. To be certain that only the ion (I) is

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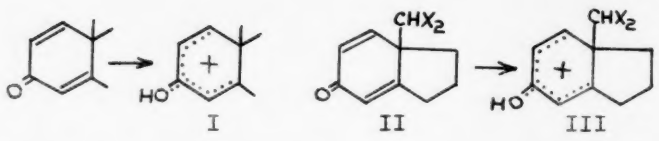
[1] Present Address.

[2] [a] R. T. Arnold and J. S. Buckley, J. Amer. Chem. Soc. 71, 1781 (1949); [b] C. Djerassi, G. Rosenkrantz, J. Romo, J. Pataki and St. Kaufmann, Ibid. 72, 4540 (1950); [c] R. B. Woodward and T. Singh, Ibid. 72, 494 (1950); [d] A. S. Dreiding, W. J. Pummer and A. J. Tomasewski, Ibid. 75, 3159 (1953); [e] C. Djerassi and T. T. Grossnickle, Ibid. 76, 1741 (1954); [f] E. N. Marvell and E. Magoon, Ibid. 76, 5118 (1954); [g] A. M. Gold and E. Schwenk, Ibid. 80, 5683 (1958); [h] S. M. Bloom, Ibid. 80, 6280 (1958); [i] H. Christol, R. Jacquier and M. Moussereron, Bull. Soc. Chim. Fr. (1959) 11; [j] J. Elks, J. F. Oughton and L. Stephenson, Proc. Chem. Soc. (1959) 6; [k] S. M. Bloom, J. Amer. Chem. Soc. 81, 4728 (1959).



I II III

responsible for the spectral change, a dienone stable to acid should be utilized. The compound, 5-keto-8-dichloromethyl-$\Delta^{4,9;6,7}$dihydroindane (II X = Cl) seemed suited for this purpose and was accordingly synthesized via a Riemer-Tiemann reaction on 5-indanol.[3] On dissolution in sulfuric acid a colorless solution was obtained, possessing maxima at 2675 Å, logϵ 4.02 and 3200 Å, logϵ 3.52, and differing markedly from the spectrum of (II X = Cl) in 95% ethanol. (Fig. 1)

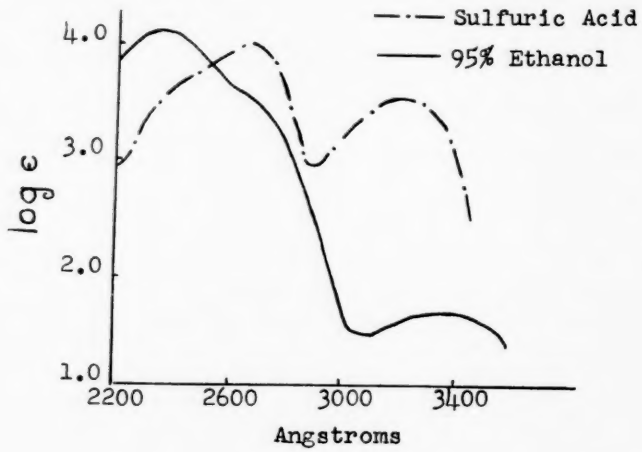


Fig. 1

[3] See R. B. Woodward, J. Amer. Chem. Soc. 62, 1208 (1940) for an earlier case. In this work 10% potassium hydroxide and a reaction time of 5 hr were used.

The dienone (II X = Cl) was recovered nearly quantitatively by diluting a sulfuric acid solution with water after one hour. The new absorption spectrum provides direct evidence for the existence of the delocalized ion (III X = Cl).

The choice of 5-keto-8-dichloromethyl-Δ^{4}, 9;6, 7 dihydroindane for this study is of sufficient interest to warrant further comment. Earlier work had shown that the migration of the alkyl chain of 5-keto-8-methyl-Δ^{4}, 9;6, 7 dihydroindane (II X = H) did not occur in acetic anhydride.[4] It seemed clear that if the migrating methyl group in (II X = H) could be so substituted to make the bond to C-8 more difficult to break, no rearrangement would occur. The choice of 5-keto-8-dichloromethyl-Δ^{4}, 9;6, 7 dihydroindane followed.

[4] S. M. Bloom, J. Amer. Chem. Soc. 81, 4728 (1959).

Tetrahedron Letters No. 21, pp. 10-13, 1959. Pergamon Press Ltd. Printed in Great Britain.

DESHYDRATATION AROMATISANTE DES 17-ETHYNYLCARBINOLS STEROIDES

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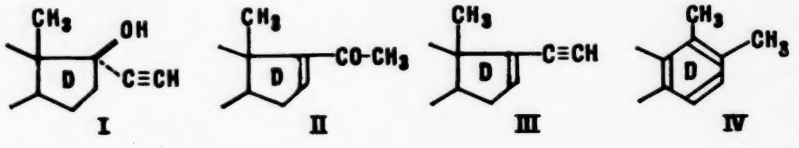
(Received 20 November 1959)

L'action de l'acide formique sur des éthynylcarbinols tertiaires fourni surtout des cétones $\alpha\beta$ éthyléniques : cette transformation classique est con sous le nom de réarrangement de Rupe[1]. On aurait pu s'attendre à ce que cet réaction, appliquée aux 17β-hydroxy 17-éthynyl stéroïdes de formule partielle (I), puisse donner accès à des dérivés du Δ^{16} 20-oxo prégnane (II). Mais il n'en est rien. Inhoffen et coll.[2], puis Hershberg et coll.[3], à partir de l'éthynyl-testostérone ont obtenu par ébullition avec l'acide formique, un



corps auquel ils attribuent la structure du 3-oxo prégna-4,16-diène-20-yne (formule partielle III). Cependant dans un article qui semble être passé inaperçu, et que nous avons nous-mêmes ignoré au début de notre travail, Hardegger et Scholz[4] ont indiqué que le 3β,17β-dihydroxy 17α-éthynyl androsta 5-ène, par traitement formique, ne fournit pas le 3β-hydroxy prégna-5,16-dièn 20-yne dont l'acétate authentique était connu[5], mais un corps pour lequel ils

1 A.W. Johnson, Acetylenic Compounds Vol. I (E. Arnold Ed., London, 1946, p. 127 et suiv.)

2 H. Inhoffen, W. Logemann, W. Holweg et A. Serini, Ber. 71, 1024 (1938)

3 E.B. Hershberg, E.P. Oliveto, C. Gerold et L. Johnson, J. Am. Chem. Soc. 73, 5073 (1951)

4 E. Hardegger et C. Scholz, Helv. Chim. Acta 28, 1355 (1945)

5 C.W. Shoppee et D.A. Prins, Helv. Chim. Acta 26, 1013 (1943)

1959

considèrent comme possible une structure partielle IV.

En plus des deux exemples mentionnés ci-dessus, nous avons soumis à l'action de l'acide formique bouillant (avec ou sans addition d'un peu d'acide para-toluène sulfonique) un certain nombre d'autres 17-éthynylcarbinols stéroïdes. Dans tous les cas, avec un rendement généralement supérieur à 50 %, nous avons obtenu des corps dans lesquels le noyau D a subi une transformation analogue, aboutissant à la structure partielle IV, pour laquelle nous présentons les arguments suivants :

1°) Par hydrogénation catalytique (par le platine Adams dans l'alcool ou l'acide acétique), on n'observe aucune fixation d'hydrogène sur cette partie de la molécule.

2°) Le spectre U.V. des corps ne possédant aucun chromophore sur les noyaux A et B (λ max 2670 Å, logε 2,55) est caractéristique d'un dérivé tétralinique[6].

3°) Les spectres I.R. de tous les corps de cette famille* présentent à 810-814 cm^{-1} la bande caractéristique des benzènes 1,2,3,4 tétrasubstitués[7].

4°) Le carbure provenant du réarrangement du 17β-hydroxy(5α)prégna-20-yne donne un spectre de R.M.N. haute résolution** qui montre l'existence de deux hydrogènes benzéniques en position ortho et de deux méthyles benzéniques également en position ortho, indépendamment d'un troisième méthyle (méthyle angulaire en 10).

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6 Voir R.A. Friedel et M. Orchin, Ultraviolet Spectra of aromatic compounds, J. Wiley and Sons éd. New-York 1951, Spectres n° 10, 11, 12 et 15.

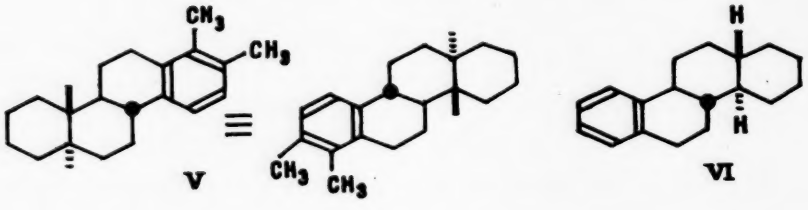
* Ces spectres ont été mesurés par J. Weinmann (Fac. de Médecine, Paris) que nous remercions vivement (Spectrographe Perkin Elmer C 13, pastilles de K Br)

7 Voir R.N. Jones et C. Sandorfy, ap. Chemical applications of Spectroscopy, Interscience Publishers, London, 1956, p. 391

** Ce résultat est dû à une étude de R.M.N. de B. Braillon et R. Romanet (Fac. des Sciences, Caen) que nous remercions très vivement.

5°) Ce même carbure, par action de l'acide nitrique-sulfurique dans le chloroforme, a fourni un dérivé dinitré (dont le pouvoir rotatoire est extraordinairement négatif).

6°) Comparé à la desoxo oestrone[8], ce même carbure possède une rotation moléculaire du même ordre de grandeur et de signe opposé (+ 235° et - 206°). On peut en effet considérer le nouveau carbure fondamental V, dont dérivent les corps que nous décrivons, comme possédant la même configuration que l'antipode optique du D-homo-oestra-triène ou du D-homo-gona-triène VI[9].



V VI

Nous avons, entre autres, préparé les dérivés suivants* :

1°) A partir de l'éthynyl-testostérone :

Le 3-oxo 17,17a-diméthyl D-homo-18-nor-androsta-4,13,15,17(17a)-tétraène, F = 165-166°. ([3] indique F = 166-169° ; $[\alpha]_D$ = - 29,9°).

2°) A partir du 3β-17β-dihydroxy prégna-5-ène-20-yne :

le 3β-hydroxy 17,17a-diméthyl D-homo-18-nor-androsta-5,13,15,17(17a)-tétraène F = 176-178°, $[\alpha]_D^{18}$ = - 286° ± 3°. ([4] indique F = 176-177°, $[\alpha]_D$ = - 287°).

Formiate : F = 166,5-170°, $[\alpha]_D^{18}$ =-271° ± 4°.

3°) A partir du 3β,17β-dihydroxy(5α)prégna-20-yne :

le 3β-hydroxy 17,17a-diméthyl D-homo-18-nor-(5α)androsta-13,15,17(17a)-triène

8 V. Prelog, L. Ruzicka et P. Wieland, Helv. Chim. Acta 28, 254 (1945)

9 J.P. Mathieu et A. Petit, Constantes Sélectionnées. Pouvoir rotatoire naturel I Stéroïdes, Masson Ed. Paris 1956, p. 3 f et suiv.

* Tous ces produits nous ont donné des analyses correctes. Les points de fusion sont déterminés au bloc Maquenne. Les pouvoirs rotatoires ont été pris dans le dioxanne, à la concentration d'environ 1 %.

F = 190°, $[\alpha]_D$ = - 74° ± 3°. Formiate : F = 155-157°, $[\alpha]_D^{19}$ = - 75° ± 3°.

4°) A partir du 17β-hydroxy-(5α)prégna-20-yne:

le 17,17a-diméthyl D-homo-18-nor-(5α)androsta-13,15,17(17a)-triène, F = 157-158,5°, $[\alpha]_D^{22}$ = - 73° ± 3°. Dérivé dinitré : F = 225-226°, $[\alpha]_D^{18}$ = 890° ± 90° (c = 0,42).

5°) A partir du 3-oxo 17β-hydroxy 17α-éthynyl oestra-5(10)-ène* :

le 3-oxo 17,17a-diméthyl D-homo-18,19-binor-androsta-4,13,15,17(17a)-tétraène**, F = 187-191,5°, $[\alpha]_D^{19}$ = - 73° ± 10° (c = 0,56).

Nous poursuivons l'étude de ce réarrangement, dont le mécanisme procède sans doute par une suite de migrations de type Wagner-Meerwein, et dont l'impulsion (driving-force) est fournie par la tendance à l'aromatisation.

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* Nous remercions la Searle C° (Chicago) pour un don gracieux d'Enovid.

** Pour tous les corps précédents, une nomenclature à partir de l'ent gonane est également possible. Dans ce dernier cas, elle est plus simple : ent 17-oxo 3,4-diméthyl D-homo-gona-1,3,5(10),13(17a)-tétraène. Sur la nomenclature des antipodes optiques stéroïdes, voir A. Horeau, J. Jacques, J.P. Mathieu et A. Petit, Bull. Soc. Chim. 22, 1304 (1955) et A. Lardon, O. Schindler et T. Reichstein, Helv. Chim. Acta 40, 676 et suiv. (1957).

Tetrahedron Letters No. 21, pp. 14-17, 1959. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF SEPIOMELANIN

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Institute of Organic Chemistry, Naples University, Naples

(Received 26 November 1959)

Sepiomelanin was obtained in a high degree of purity; the analytical study of this natural pigment gives an interesting confirmation of the indolequinone theory.[1,2] The black pigment from Sepia officinalis was purified by several washings with 1% HCl, exhaustive extraction by hot acetone, prolonged boiling with concentrated HCl(about 150 hours). Finally the pigment was washed first with water and then with acetone; after drying in vacuo at 80°C over P_2O_5 it was obtained as an ashless black powder, with a very small sulphur content(0.2%).

For analysis, samples were dried in vacuo at 110°C over P_2O_5(17 hours) and weighed in sealed tubes. The following results were obtained:

C, 64.08 H, 3.00 N, 8.52

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[1] A.D.Bu'Lock and J.Harley-Mason, J.Chem.Soc. 703(1951).

[2] H.S.Mason, Pigment Cell Biology, Academic Press,New York (1959).

1959

Very similar results were obtained with samples isolated in the same way from different specimens of Sepia officinalis.

Sepiomelanin, suspended in ether, reacted with diazomethane; this reagent was added until it was no more absorbed. The pigment was then washed with methanol, dried in vacuo at 110 °C over P_2O_5 (17 hours), and analyzed. The following results were obtained:

C, 65.57 H, 4.75 N, 7.82 O, 22.00 $-OCH_3$, 17.43

The analytical results of samples from different specimens of Sepia officinalis were found to be in a surprisingly good agreement. [3] Methylated sepiomelanin gave a positive test for $-O-CH_2O-$ group (gallic acid in conc. H_2SO_4).

The examination of the analytical results of sepiomelanin, before and after reaction with diazomethane, showed an oxygen content higher than that calculated for a polymer of indole-5,6-quinone. Since no water was contained in the analyzed sepiomelanin, because of its exhaustive drying, presence of carboxyl groups was suspected. In order to give a definite proof of their existence, sepiomelanin was treated with saturated solution of HCl in methanol at room temperature: an ester was so obtained with a 4% methoxyl content. This value indicated the presence of

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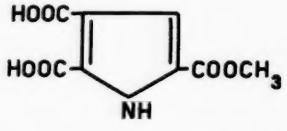
[3] When considering the fact that all the sepiomelanin samples are very difficult to be burnt.

one carboxyl group about every fifth indolequinone nucleus.

The pigment after reaction with diazomethane was suspended in cold 2N K_2CO_3 and oxidized with $KMnO_4$: pyrrole-2,3-dicarboxylic acid, pyrrole-2,4,5-tricarboxylic acid and pyrrole-2,3,4,5-tetracarboxylic acid, normal oxidative degradation products of sepiomelanin,[4,5,6] could not be detected by paper chromatography. Neverthless, after alkaline hydrolysis of crude oxidation product, pyrrole-2,4,5-tricarboxylic acid was identified. The result showed that partial methyl-ester of pyrrole-2,4,5-tricarboxylic acid, almost certainly the 2-carbomethoxy-pyrrole-4,5-dicarboxylic acid(I)



I

was contained in the degradation products mixture of methylated sepiomelanin. Therefore, pyrrole-2,4,5-tricarboxylic acid must derive from a 2-carboxy-indole-5,6-quinone unit, and sepiomelanin can be formulated as a copolymer of indole-5,6-quinone and 2-carboxy-indole-5,6-quinone.

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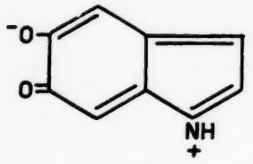
[4] L.Panizzi and R.A.Nicolaus, Gazz.Chim.Ital. 82,435(1952).

[5] R.A.Nicolaus and L.Mangoni, Gazz.Chim.Ital. 85,1397(1955).

[6] R.A.Nicolaus, A.Vitale and M.Piattelli, Rend.Acc.Sc.fis. e mat.vol.XXVI, 3(1959).

All the analytical data are in good agreement for a polymer in which the units (II) and (III) are present in the ratio 4:1, respectively. Similarly, for the methylated sepiomelanin the units (IV) and (V) should be in the ratio 1:4.



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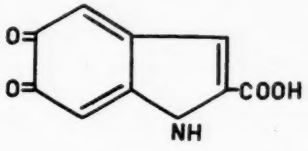
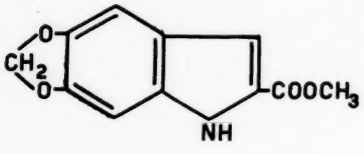
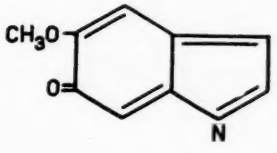


III



IV



V

On the basis of the analytical data, the presence of some reduced indolequinone unit cannot be excluded. It is not yet determined which positions of the indolequinone units play a part in the building up of the polymer : useful indications shall be desumed from the study of degradation products of methylated sepiomelanin.

Full details on this investigation will be published in the Rendiconto dell'Accademia delle Scienze Fisiche e Matematiche della Società Nazionale di Scienze, Lettere ed Arti in Napoli.

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DIASTEREOISOMERIC BENZYLIDENENUCLEOSIDES

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Department of Chemistry, Washington University, St. Louis 30, Mo.

(Received 9 November 1959)

THE specific rotation of benzylideneguanosine (I) was first reported by Michelson and Todd,[1] although the compound had been synthesized previously by two other groups of investigators.[2] In attempting to repeat the synthesis of this compound, Lipkin and McElheny[3] obtained a benzylideneguanosine (Ib) which differed from the 2':3'-isomer of Michelson and Todd[1] (Ia) in both its specific rotation and its solubility in pyridine. It was suggested at the time[3] that Ib was isomeric with Ia either because of a difference in the position of substitution of the benzylidene group or because of a difference in stereochemical configuration of the benzylidene carbon atom. It now is demonstrated conclusively that the latter explanation is the correct one. Furthermore, two 2':3'-benzylideneuridines (II) were

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[1] A. Michelson and A. R. Todd, J. Chem. Soc. 2476 (1949); D. M. Brown, L. J. Haynes and A. R. Todd, J. Chem. Soc. 3299 (1950).

[2] H. Bredereck and E. Berger, Ber. 73, 1124 (1940); J. M. Gulland and W. G. Overend, J. Chem. Soc. 1380 (1948).

[3] D. Lipkin and G. C. McElheny, Nature, Lond. 167, 238 (1951).

prepared and it was proved that their isomerism is also due only to a difference in the configuration of the benzylidene carbon. Experimental evidence for the existence of such diastereoisomerism in simpler benzylidene-substituted sugar derivatives has been presented.[4]

A benzylideneuridine (IIa) was prepared by shaking benzaldehyde and uridine with anhydrous zinc chloride for 7 days at 5°. Yield, 68%; m. p. 191-191.5°; $[\alpha]_D^{27}$ -93.3°($HCONMe_2$, c 1.22). Found: C, 57.73; H, 4.68; N, 8.49. $C_{16}H_{16}N_2O_6$ requires C, 57.83; H, 4.85; N, 8.43%. By carrying out the reaction at 26° for 20 hrs. and then at 100° for 1 hr., an isomer (IIb) of the above was obtained. Yield, 74%; m. p. 193-194°; $[\alpha]_D^{26}$ -57.9°($HCONMe_2$, c 1.35). Found: C, 57.86; H, 4.82; N, 8.23. Gulland and Smith reported no specific rotation, but gave m. p. 189-190°, for II.[5] Compounds IIa and IIb give different X-ray powder patterns and differ somewhat in their infrared spectra (KBr disks). Compound IIb does not depress the m.p. of IIa.

A sample of each of the isomers was subjected to Purdie methylation and the benzylidene group then was removed at room

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[4] A review of the literature on this subject is given by B. Dobinson, A. B. Foster and M. Stacey, Tetrahedron Letters 1 (1959).

[5] J. M. Gulland and H. Smith, J. Chem. Soc. 338 (1947).

temperature by means of 48°/o hydrofluoric acid.[6] The resulting methylated uridines (III) were found to be oxidizable by periodate. Samples of III were treated with hydrazine[7] and the O-methylriboses thus obtained were shown to be identical with authentic 5-O-methylribose[8] by means of paper chromatography and paper electrophoresis.[9,10] These observations demonstrated that IIa and IIb are 2';3'-benzylidenenucleosides. In order to demonstrate that changes in the parent nucleoside, such as an α-β or a furanoside-pyranoside interconversion, did not take place during the preparation of the benzylidenenucleosides, IIa and IIb were hydrolyzed by means of 48°/o hydrofluoric acid.[6] The recovered nucleosides were shown to be identical with authentic uridine by means of paper chromatography, measurements of their specific rotation, mixed melting points, ultraviolet absorption spectra and X-ray powder patterns.

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[6] D. Lipkin, W. H. Cook and R. Markham, J. Amer. Chem. Soc., in press.

[7] F. Baron and D. M. Brown, J. Chem. Soc. 2855 (1955).

[8] D. Lipkin, E. B. Rauch and W. H. Hunter, unpublished results.

[9] D. M. Brown, D. I. Magrath and A. R. Todd, J. Chem. Soc. 1442 (1954)

[10] G. R. Barker, T. M. Noone, D. C. C. Smith and J. W. Spoors, J. Chem. Soc. 1327 (1955).

It is worth noting that IIa is converted to IIb at room temperature by means of anhydrous zinc chloride in benzaldehyde solution. The reverse interconversion does not take place at 5°. Both isomers are stable, however, at room temperature in the presence of a methanol suspension of silver oxide.

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Compounds Ia and Ib were prepared by using the two different reaction conditions described for the preparation of IIa and IIb.[11] Using essentially the same procedures as those which were used with II, including the recovery of guanosine by hydrolysis of Ia and Ib with 48°/o hydrofluoric acid, it was demonstrated that the two isomers are diastereoisomeric 2':3'-benzylideneguanosines in which the only difference is the configuration of the benzylidene carbon.

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[11] Many unsuccessful attempts were made in our laboratory to synthesize the Michelson-Todd isomer. Only after we recognized the fact that the average room temperature in Cambridge, England, was much lower than in Saint Louis, Missouri, were we able to obtain the low temperature isomer without any difficulty.

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ON THE MECHANISM OF THE FORMOSE REACTION

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IN 1861 Butlerow[1] first noted the formation of sugar-like substances when formaldehyde is treated with mild base. Since that time numerous investigations of this reaction have been undertaken,[2] and many mechanisms have been suggested for the process, but to date no mechanism appears to have been formulated which does not employ "active formaldehyde" or some other ill-defined species. It is the purpose of this communication to call attention to the considerable body of data available on this reaction and to point out a mechanism which is consistent with such data and which is also consistent with chemical experience.

Although a heterogeneous mixture of products is usually obtained on treatment of formaldehyde solutions with base, conditions have been realized in which as much as 50% of the original formaldehyde has been converted to glycolaldehyde.[3] Furthermore, trioses, tetroses, etc., could easily arise

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[1] A. Butlerow, C. R. Acad. Sci., Paris 53, 145 (1861).

[2] For a short review with leading references, cf. W. Langenbeck, Tetrahedron 3, 185 (1958).

[3] W. Langenbeck, Angew. Chem. 66, 151 (1954).

from aldol condensations involving glycolaldehyde as the active methylene component and formaldehyde, glycolaldehyde, etc., as the carbonyl component. For this reason it has long been obvious that the formation of glycolaldehyde from formaldehyde is the process to be explained, and we will not further consider the subsequent condensation reactions in this paper.

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The reaction of two formaldehyde molecules by an "aldol condensation" mechanism is of course very unlikely, and the finding that there is a long induction period in the formose reaction[4] suggests that if such a direct process does occur it must be very slow. However, kinetic studies have shown that after this induction period a rapid reaction ensues.[4] This suggests an autocatalytic process, and this has been confirmed by the finding that the addition of glycolaldehyde, glyceraldehyde, or dihydroxyacetone causes the induction period to disappear, the reaction starting immediately but at the same rate as that observed in the fast part of the normal formose reaction. This has led to the suggestion that there are two processes by which the formaldehyde condensation occurs: (1) a slow direct condensation, possibly involving a formyl anion, but forming glycolaldehyde at an indetectable rate. (2) a fast reaction, catalyzed by glycolaldehyde, in which formaldehyde condenses to a second molecule of glycolaldehyde.

The first reaction is certainly interesting, but it is relatively inacessible for study if it proceeds at an indetectable rate, and if the rate is slow the reaction is not inconceivable as formulated, being related

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[4] Careful kinetic studies, with references to the earlier work, are reported by E. Pfeil and G. Schroth, Ber. 85, 293 (1952).

to other cases in which some moderate acidity of hydrogens on a double bond has been observed.[5] The high rate of the second process strongly indicates, however, that some more usual types of reaction are involved in its mechanism. We wish to point out that, although minor modifications in details are possible, the following series of simple condensations and tautomerizations suffice to rationalize the process:

(1) $CH_2O + HOCH_2\text{-}CHO \longrightarrow HOCH_2\text{-}CHOH\text{-}CHO$

(2) $HOCH_2\text{-}CHOH\text{-}CHO \rightleftharpoons HOCH_2\text{-}CO\text{-}CH_2OH$

(3) $CH_2O + HOCH_2\text{-}CO\text{-}CH_2OH \longrightarrow HOCH_2\text{-}CHOH\text{-}CO\text{-}CH_2OH$

(4) $HOCH_2\text{-}CHOH\text{-}CO\text{-}CH_2OH \rightleftharpoons HOCH_2\text{-}CHOH\text{-}CHOH\text{-}CHO$

(5) $HOCH_2\text{-}CHOH\text{-}CHOH\text{-}CHO \longrightarrow HOCH_2\text{-}CHO + HOCH_2\text{-}CHO$

The first aldol condensation is unexceptionable, and the tautomerization of glyceraldehyde to dihydroxyacetone through the common enol is also well known. This can of course undergo a second aldol condensation to form the keto tetrose. The crucial step is the next one, in which this keto tetrose tautomerizes to the aldotetrose. This is simply the aldol condensation product of two glycolaldehydes, and by a simple reverse aldol reaction can regenerate the original glycolaldehyde and liberate the new one, which has thus been synthesized from two formaldehyde molecules.

This mechanism is certainly consistent with the operation of small amounts of glycolaldehyde, glyceraldehyde, or dihydroxyacetone in eliminating the induction period but not affecting the rate of the fast process, assuming that a steady state concentration of these intermediates would be established because of the competing further condensations.

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[5] R. Breslow, J. Amer. Chem. Soc. 80, 3719 (1958).

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Furthermore, this mechanism explains why benzoylcarbinol can give both an immediate reaction and a faster reaction when it is added as catalyst to the formaldehyde reaction mixture,[3] for it can function in place of glycolaldehyde, thus eliminating the induction period, and condensation reactions involving benzoylcarbinol might well be even faster than those involving glycolaldehyde, a presumption which is supported by the observation that m- and p-cyanobenzoylcarbinol are still better catalysts, while the p-methoxy compound is somewhat worse.

Many other catalysts are known for this reaction,[2] and most of them, e.g. benzoin, could not function in place of glycolaldehyde in our mechanism, a factor which has undoubtedly contributed to the overlooking of this mechanism previously. However, in all these cases the effect is to shorten the induction period only, and the eventual reaction rate is not accelerated, but is identical with that in the fast part of the normal reaction. Thus we suggest that many of these other catalysts facilitate the formation of the first molecule of glycolaldehyde, but that the catalysts are not involved in the fast section of the reaction. It is possible to suggest reasonable mechanisms for all of these cases by which the first glycolaldehyde molecule might be produced more rapidly, but these will not be outlined here since our prime concern is with the second fast part of the reaction.

It has also been found that the reaction is very dependent on the metal ion involved in the base,[5] being rapid with thallium or lead hydroxides, relatively fast with calcium hydroxide, and of negligible importance with sodium or potassium hydroxide. It has even been found that in the presence of an appropriate metal ion the reaction can be acid catalyzed. All of this

is explicable in terms of the well known stabilizing effect of chelating ions on enediols, which are postulated intermediates in the tautomerization and condensation steps of our mechanism. Finally, the uniqueness of formaldehyde in this reaction derives from the fact that it alone among the aldehydes can condense to an acyloin with an active methylene group, and therefore, it alone can lead to an autocatalytic reaction.

The function of glycolaldehyde in this mechanism is clearly analogous to that of cyanide ion in the benzoin condensation. A carbonion is involved (in this case the enolate ion of glycolaldehyde) whose carbon also has carbonyl-like character (in this case by tautomerization to a true carbonyl group). The prediction of other catalyses of this type and some other predictions based on our suggested mechanism are currently under investigation.

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